Cl_3CNO_2 = PS

BEILSTEINS HANDBUCH DER ORGANISCHEN CHEMIE

VIERTE AUFLAGE

ZWEITES ERGÄNZUNGSWERK

DIE LITERATUR VON 1920—1929 UMFASSEND

HERAUSGEGEBEN VON DER

DEUTSCHEN CHEMISCHEN GESELLSCHAFT

BEARBEITET VON

FRIEDRICH RICHTER

ERSTER BAND

ALS ERGÄNZUNG DES ERSTEN BANDES DES HAUPTWERKES

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Ausbreitung auf Wasser bei 20°: HARKINS, FELDMAN, *Am. Soc.* **44**, 2671. Grenzflächenspannung zwischen Nitromethan und Wasser bei 20°: HAR., CLARK, ROBERTS, *Am. Soc.* **42**, 704. Dichte und Oberflächenspannung von Lösungen in Benzol bei 25°: HAMMICK, ANDREW, *Soc.* **1929**, 758. Elektrische Leitfähigkeit einer Lösung von Nitromethan in Schwefelsäuremonohydrat bei 12°: CHERBULIEZ, *Helv.* **6**, 285. Leitfähigkeit und Ionisation von Lösungen von Kaliumjodid in Nitromethan zwischen 0° und 85°: PHILIP, OAKLEY, *Soc.* **125**, 1193. Leitfähigkeit der Lösungen von Halogenwasserstoffen in trocknem und feuchtem Nitromethan: HLASKO, MICHALSKI, *C.* **1927** I, 2803. Einfluß auf die Beweglichkeit der Ionen verschiedener Salze: ULICH, *Fortsch. Ch., Phys.* **18** [1924/26], 600; LATTEY, *Phil. Mag.* [7] **6**, 263. Elektrische Leitfähigkeit von Tetramethylammoniumnitrat in Nitromethan bei 25°: WALDEN, *Z. El. Ch.* **26**, 74. Potentialdifferenzen an der Trennungsfläche wäßr. Lösung/Luft bei 25°: FRUMKIN, DONDE, KULVARSKAJA, *Ph. Ch.* **123**, 334.

Chemisches Verhalten. Mechanismus und Geschwindigkeit der Umwandlung von Isonitromethan in Nitromethan bei Einw. von Salzsäure auf Natriumisonitromethan bei 0° und —23,8° in verd. Methanol, beobachtet an Hand der Änderung der Leitfähigkeit: BRANCH, JAXON-DEELMAN, *Am. Soc.* **49**, 1770. Reduktion mit Titantrichlorid in siedender wäßrig-alkoholischer Salzsäure: HENDERSON, MACBETH, *Soc.* **121**, 901. Zur Geschwindigkeit der Reduktion durch Blei und Essigsäure vgl. PRINS, *R.* **44**, 1051. Kinetik der Chlorierung in wäßr. Salzsäure bei 69,85° und der Bromierung in wäßr. Bromwasserstoffsäure und Salzsäure-Lösung bei 49,9°, 59,9° und 69,85°: JUNELL, *Ph. Ch.* [A] **141**, 85. Reaktion mit Berylliumchlorid: FRICKE, HAVESTADT, *Z. anorg. Ch.* **146**, 122. Die Natriumverbindung gibt bei der Einw. von Benzil in Alkohol Äthylbenzoat, geringe Mengen Natriumbenzoat und ein gelbbraunes, natriumhaltiges Pulver, das bei der Einw. von verd. Mineralsäuren ω-Nitrostyrol und β-Nitro-α-phenyl-äthylalkohol liefert (KASIWAGI, *C. r.* **184**, 36; *Bl. chem. Soc. Japan* **2**, 204). Nitromethan liefert beim Behandeln mit Glykolaldehyd in Wasser unter Zusatz von Kaliumdicarbonat auf dem Wasserbad, Reduzieren mit Aluminiumamalgam unter Wasserkühlung und nachfolgendem Erwärmen mit Natriumnitrit in salzsaurer Lösung geringe Mengen Glycerin (PICTET, BARBIER, *Helv.* **4**, 925). Gibt mit Glucose in analoger Reaktion d-Gluco-α-heptit (PI., BA.). Über das Verhalten gegen Glycerinaldehyd oder l-Arabinose vgl. PI., BA. Bei der Einw. von Zinkstaub auf Nitromethan und Protocatechualdehyd in 30%iger Essigsäure entsteht 3.4-Dioxy-benzaldoxim-N-methyläther (KANAO, *C.* **1929** I, 2974). — Nitromethan gibt mit Pikrinsäure in alkal. Lösung eine rote Färbung (WEISE, TROPP, *H.* **178**, 135).

Salze und additionelle Verbindungen. Natriumsalz. Explodiert besonders leicht unter Feuererscheinung beim Befeuchten (HEUBERGER, *C.* **1926** I, 3017). — $Ca(CH_2O_2N)_2$. *B.* Aus äther. Nitromethan-Lösung bei der Einw. von Calciumhydrid (DURAND, HOUGHTON, *C. r.* **180**, 1034). — $CH_3O_2N + TiCl_4$. Gelbe Krystalle (aus Tetrachlorkohlenstoff oder durch Sublimation im Vakuum). F: 48° (REIHLEN, HAKE, *A.* **452**, 60). Raucht stark an der Luft. Löst sich in Wasser unter Zischen. Beim Behandeln mit viel Nitromethan entsteht die nachfolgende Verbindung. — $CH_3O_2N + TiO_2 + TiCl_4$. *B.* Aus der Verbindung $CH_3O_2N + TiCl_4$ durch Behandeln mit viel Nitromethan (REI., HAKE). Feiner gelblicher Niederschlag. Raucht schwach an der Luft. Löst sich klar in Wasser.

Chlornitromethan $CH_2O_2NCl = CH_2Cl \cdot NO_2$ (H 76). Zu Tränen reizendes Öl (TROEGER, NOLTE, *J. pr.* [2] **101**, 143). — Liefert bei der Kondensation mit Formaldehyd 2-Chlor-2-nitro-propandiol-(1.3) und geringe Mengen 2-Chlor-2-nitro-äthanol-(1) (WILKENDORF, TRÉNEL, *B.* **56**, 613, 616). Bei der Einw. von benzolsulfinsaurem Natrium in Alkohol im Rohr wurde einmal Nitromethyl-phenyl-sulfon(?) erhalten (TROE., N.).

Trichlornitromethan, Chlorpikrin $CO_2NCl_3 = CCl_3 \cdot NO_2$ (H 76; E I 20). *B.* Aus Trichlornitrosomethan beim Erhitzen mit oder ohne Sauerstoff oder bei der Oxydation mit Chromtrioxyd in Eisessig (PRANDTL, SENNEWALD, *B.* **62**, 1764). Bei der Oxydation von o- und p-Nitro-phenol, 2.4-Dinitro-phenol (ORTON, MCKIE, *Soc.* **119**, 33; SEYEWETZ, CHAIX, *Bl.* [4] **41**, 197), Trinitrotoluol (O., MCK.), Pikrinsäure und 2.4-Dinitro-naphthol-(1)-sulfonsäure-(7) (Naphtholgelb S) (SEY., CH.) mit Natriumhypochlorit. — Darstellung durch Chlorierung von Pikrinsäure in sodaalkalischer Lösung: O., MCK. Aus Sicherheitsgründen geht man besser statt von der schwer löslichen Pikrinsäure von dem leicht löslichen Calciumpikrat aus, das man in Gegenwart von überschüssigem Chlorkalk mit Wasserdampf destilliert (TRUMBULL und Mitarbeiter, *J. ind. Eng. Chem.* **12**, 1068; *C.* **1921** II, 408).

Dampfdruck zwischen +35° (40,1 mm) und —20° (1,5 mm): BAXTER, BEZZENBERGER, WILSON, *Am. Soc.* **42**, 1388; vgl. a. BLASZKOWSKA-ZAKRZEWSKA, *Roczniki Chem.* **8**, 226; *C.* **1929** I, 3076; HERBST, *Koll. Beih.* **23**, 330; *C.* **1926** II, 2544; zwischen 98,0° (502,1 mm) und 105,0° (597,0 mm): BL.-Z. Flüchtigkeit: LEITNER, *Militärw. tech. Mitt.* **57** [1926], 665. Parachor: MUMFORD, PHILLIPS, *Soc.* **1929**, 2118. Adsorption der Dämpfe an Tierkohle:

ALEXEJEWSKI, Ж. 55. 415; C. 1925 II, 642; an aktiver Kohle: URBAIN, C. r. 180, 64; an trockner und an wasserhaltiger aktiver Kohle: H., Bio. Z. 115, 216; 118, 107. Geschwindigkeit der Adsorption an Holzkohle: HARNED, Am. Soc. 42, 374. Wärmetönung bei der Adsorption von Chlorpikrin-Dampf an Holzkohle bei 0°: KEYES, MARSHALL, Am. Soc. 49, 163. Adsorption an Faserstoffe: A., C. 1929 II, 708. Absorption durch Gummi und gummiertes Gewebe: RECTOR, Ind. Eng. Chem. 15, 1132; C. 1924 I, 2390. Chlorpikrin ist in Methanol, Alkohol, Aceton, Benzol, Essigsäure in jedem Verhältnis löslich (PIUTTI, G. 51 I, 145). 100 cm³ Wasser lösen bei 0° 0,2272, bei 25° 0,1621, bei 75° 0,1141 g Chlorpikrin; 100 g Chlorpikrin lösen bei 32° 0,1003 g, bei 55° 0,2265 g Wasser (THOMPSON, BLACK, J. ind. Eng. Chem. 12, 1067; C. 1921 I, 350). Thermische Analyse des binären Systems mit Stickstofftetroxyd (Eutektikum bei —79,5° und 8% Stickstofftetroxyd): PASCAL, Bl. [4] 33, 544; des binären Systems mit Tetryl (N-Nitro-N-methyl-2.4.6-trinitro-anilin): JEFREMOW, TICHOMIROWA, C. 1929 I, 745. Bildet azeotrope Gemische mit Methylcyclohexan (Kp: 100,75°; 29% Chlorpikrin) (LECAT, Ann. Soc. scient. Bruxelles 47 I, 24; C. 1927 II, 226), Alkohol (Kp: 77,4°; ca. 35% Chlorpikrin), Propylalkohol (Kp: 94,0°; 58,5% Chlorpikrin), Isopropylalkohol (Kp: 82,0°; 33,5% Chlorpikrin), Isobutylalkohol (Kp: 102,05°; 67,5% Chlorpikrin), Butylalkohol (Kp: 106,2°; 75% Chlorpikrin), Dimethyläthyl-carbinol (Kp: 97,2°; 63% Chlorpikrin), Isobutylcarbinol (Kp: 110.0°; 85% Chlorpikrin) und Allylalkohol (Kp: 93,9°; 60% Chlorpikrin) (L., R. 46, 243).

Chlorpikrin wird im zerstreuten Licht allmählich gelb, am Sonnenlicht rotbraun und zersetzt sich in Methanol, Alkohol und Aceton am Sonnenlicht unter Bildung von Ammoniumchlorid (PIUTTI, G. 51 I, 145). Zerfällt im ultravioletten Licht allmählich in Phosgen und Nitrosylchlorid (PI., MAZZA, G. 57, 610; C. 1927 I, 240). Wirkt auf organische Lösungsmittel am Licht oxydierend, chlorierend und nitrierend; so entsteht z. B. aus Essigsäure Oxalsäure und Chloressigsäure, aus Salicylsäuremethylester 3-Chlor-salicylsäure-methylester neben etwas Oxalsäure, aus Toluol o-Nitro-toluol und Benzoesäure, aus Phenol 4.6-Dichlor-2-nitro-phenol (PI., BADOLATO, R. A. L. [5] 33 I, 476). Korrosion von Metallen durch Chlorpikrin-Dampf: ALEXEJEWSKI, ALEXEJEW, C. 1929 II, 793. Leitet man Chlorwasserstoff durch Chlorpikrin bei 100° und führt das entstandene Gasgemisch über Bimsstein bei 400°, so entstehen Phosgen, Nitrosylchlorid, Stickoxyd und geringe Mengen Hexachloräthan (SILBERRAD, C. 1922 I, 403). Chlorpikrin liefert beim Erhitzen mit rauchender Schwefelsäure (20% SO_3) auf 100° Phosgen (SECAREANO, Bl. [4] 41, 630). Einw. von Hydrazin in wäßrig-alkoholischer Kalilauge bei 13—13,5°: MACBETH, PRATT, Soc. 119, 1358. Beim Aufbewahren von Chlorpikrin mit Titantetrachlorid entsteht die Verbindung $TiCl_4+2NOCl$ (REIHLEN, HAKE, A. 452, 63). Gibt mit Benzol in Gegenwart von Quecksilberchlorid und Aluminium bei 45° auf dem Wasserbad Triphenylnitromethan (RÂY, Soc. 117, 1339). Bei der Einw. von Natriummethylat-Lösung entstehen unter heftiger Reaktion Orthokohlensäure-tetramethylester und geringe Mengen Kohlensäure-dimethylester (v. HARTEL, B. 60, 1841). Geschwindigkeit der Reaktion mit Natriummethylat in Methanol: TRONOW, GERSCHEWITSCH, Ж. 60, 179; C. 1928 II, 772. Läßt man Chlorpikrin auf Äthylmercaptan in alkoh. Kalilauge unter Kühlung einwirken, so entsteht Diäthyldisulfid; analog reagieren Thiophenol und Thio-p-kresol (NEKRASSOW, MELNIKOW, B. 62, 2093; Ж. 61, 2052). Reagiert in konz. Natronlauge bei 50—60° lebhaft mit Phenol unter Rotfärbung und Bildung von Salicylaldehyd, Salicylsäure, p-Oxy-benzaldehyd, p-Oxy-benzoesäure und Pararosolsäure (BERLINGOZZI, BA., R. A. L. [5] 33 I, 291). Chlorpikrin liefert bei der Einw. auf Natriummalonester in Alkohol als Hauptprodukt Äthan-tetracarbonsäure-(1.1.2.2)-tetraäthylester (INGOLD, POWELL, Soc. 119, 1227, 1231). Gibt beim Erhitzen mit Natriumcyanessigester in Alkohol auf 100° 1.2.3-Tricyan-cyclopropan-tricarbonsäure-(1.2.3)-triäthylester (I., Po.). Geschwindigkeit der Reaktion mit Pyridin bei 16—18°: TRONOW, Ж. 58, 1287, 1289; C. 1927 II, 1145; T., GE.; mit Piperidin: T. Gasentwicklung bei der Einw. von Methylmagnesiumjodid auf Chlorpikrin in Dibutyläther bei 70°: GILMAN, FOTHERGILL, Bl. [4] 45, 1135. Wärmetönung der Reaktionen mit Äthyl- und Phenylmagnesiumbromid in Äther: LIFSCHITZ, KALBERER, Ph. Ch. 102, 408. Bei der Umsetzung mit Phenylmagnesiumbromid beobachtet man eine besonders helle Luminescenz (LI., K.).

Tränenreizende Wirkung von Chlorpikrin: DUFRAISSE, BONGRAND, C. r. 171, 819; BERTRAND, C. r. 171, 965. Unerträglichkeitsgrenze der Reizwirkung auf den Menschen: FLURY, Z. exp. Med. 13, 567; C. 1921 III, 565; LEHRECKE, C. 1927 I, 2598. Giftwirkung beim Säugetier: MAYER, PLANTEFOL, VLÈS, C. r. 171, 1397; GILDEMEISTER, HEUBNER, C. 1921 III, 374; AUER, C. 1922 I, 834. — Zur Verwendung von Chlorpikrin (auch Klop und Aquinite genannt) als Kampfstoff vgl. VAN NIEUWENBURG, C. 1922 IV, 984 und die bei Dichlordiäthylsulfid (Syst. No. 23) zitierte Buchliteratur. Chlorpikrin wird durch eine wäßr. Lösung von Schwefelleber und Seifenlauge unschädlich gemacht (DESGREZ, GUILLEMARD, SAVÈS, C. r. 171, 1179; D., G., LABAT, C. r. 172, 342). — Wirkung auf die Keimfähigkeit von Samen: MIÈGE, C. r. 172, 170; auf Schimmelpilze: MATRUCHOT, SEE, C. 1920 I, 741; auf einige Hefearten: MEIER, C. 1927 II, 1360; auf Bakterien: BERTRAND, ROSENBLATT,

Cl_3CNO_2 = PS

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VIERTE AUFLAGE

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BEILSTEIN-INSTITUT FÜR LITERATUR DER ORGANISCHEN CHEMIE

BEARBEITET VON
FRIEDRICH RICHTER

UNTER STÄNDIGER MITWIRKUNG VON
RUDOLF OSTERTAG
GÜNTHER AMMERLAHN MARGARETE BAUMANN
ERNST BEHRLE MARIA KOBEL

ERSTER BAND

ERSTER TEIL

SPRINGER-VERLAG
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1958

Dichlornitromethan $CHCl_2NO_2 = CHCl_2 \cdot NO_2$. *B.* Beim Einleiten von Chlor in die wss. [Lösung] von nitroessigsaurem Kalium (STEINKOPF, KÜHNEL, *B.* 75 [1942] 1329). — Öl. Kp: 106—107°.

Trichlornitromethan, Chlorpikrin $CCl_3NO_2 = CCl_3 \cdot NO_2$ (H 76; E I 20, II 41). Zusammenfassende Übersicht bis 1931: JACKSON, *Chem. Reviews* 14 251. — *B.* Durch Behandeln von Nitromethan mit Hypochlorit-Lösung (Comm. Solv. Corp., A.P. 2181411 [1937], 2365981 [1941]; *C. A.* 1940 1993, 1946 3126). Zur Bildung aus Calciumpikrat und Chlor (E II 41) unter Kühlung vgl. FRAHM, *R.* 50 [1931] 1126; Great-Western Electro-Chem. Co., A.P. 1996388 [1932]; *C.* 1935 II 3702. Durch Nitrieren von Chloroform (vgl. H 76) mit wasserfreier HNO_3 bei 140—150° unter Druck (DĂNĂILA, SOARE, *Bulet.* 35 [1932] 53; *C.* 1934 II 2133).

Physikalische Eigenschaften

Kp_{757}: 112° (MATHIEU, MASSIGNON, *Ann. Physique* [11] 16 [1941] 9); Kp_{755}: 109,5—110° (REDEMANN, CHAIKIN, FEARING, *Am. Soc.* 70 [1948] 2582); Kp_{739}: 111,2° (PENDL, REITZ, SABATHY, *Pr. indian Acad.* [A] 8 [1938] 511; *C.* 1939 II 1855); Kp_{729}: 111° (MOHLER, *Helv.* 21 [1938] 788); Kp_{77}: 50,0° (WITTEK, *Z. physik. Chem.* [B] 51 [1942] 104); Kp_{70}: 47,4—48,4° (PE., R., SA.). Dampfdruck zwischen 25,5° (24 mm) und 55,0° (100 mm): GOULD, HOLZMAN, NIEMANN, *Anal. Chem.* 19 [1947] 205. D_4^{20}: 1,6558 (RE., CH., F.); D_4^{25}: 1,6483 (SMYTH, WALLS, *J. chem. Physics* 3 [1935] 557). n_D^{20}: 1,4611 (RE., CH., F.); n_D^{25}: 1,4596 (SM., WA.). Leidenfrostsches Phänomen: BLASZKOWSKA-ZAKRZEWSKA, *Bl. Acad. polon.* [A] 1930 188; *C.* 1930 II 3379. Ultraviolett-Absorptionsspektrum in Hexan: MOHLER, PÓLYA, *Helv.* 19 [1936] 285, 1237, 1241; MO., *Helv.* 20 [1937] 282; MO., SORGE, *Helv.* 22 [1939] 238. Infrarotspektrum: CORIN, *J. Chim. phys.* 33 [1936] 470, 471; MA., MA., *Ann. Physique* [11] 16 10, 13; *C. r.* 212 [1941] 1085. Ramanspektrum: MÉDARD, *J. Chim. phys.* 32 [1935] 136; PE., R., SA.; MA., MA., *Ann. Physique* [11] 16 10, 12; *C. r.* 212 1085. *Dipolmoment*: 1,30 D (ε; Heptan oder Benzol) (SM., WA.), 1,91 D (ε; Hexan) (MOHLER, *Helv.* 21 788), 1,88 D (ε; Dampf) (SM., MCALPINE, *Am. Soc.* 56 [1934] 1608; SM., WA.). Magnetische Susceptibilität: COURTY, *C. r.* 224 [1947] 1638.

Verteilung zwischen Olivenöl und Wasser bei 20°: MACY, *J. ind. Hyg.* 30 140; *C. A.* 1948 6619.

E II 42, Z. 12—13 v. o. streiche „ ; des binären Systems mit Tetryl (N-Nitro-N-methyl-2.4.6-trinitro-anilin): JEFREMOW, TICHOMIROWA, *C.* 1929 I 745".

Azeotrope Gemische, die Chlorpikrin enthalten, s. in der untenstehenden Tabelle. Dampfdruck der binären Systeme mit Toluol und Äther: RABCEWICZ-ZUBKOWSKI, *Roczniki Chem.* 12 161; *C.* 1932 II 2299. Diffusion in Luft bei 25°: KLOTZ, MILLER, *Am. Soc.* 69 [1947] 2557. Zur Adsorption an Aktivkohle (E II 42) vgl. ferner ENGEL, *Z. ges. Schieß-Sprengstoffw.* 24 [1929] 451, 495; *C.* 1930 I 1281; DUBININ, *Ж.* 62 [1930] 690; KUBELKA, *Koll. Z.* 55 [1931] 133; MACY, *J. phys. Chem.* 35 [1931] 1406; ALEXEJEWSKI, PIKASIN, *Z. obšč. Chim.* 2 [1932] 331; TSCHANG-HAN-LIANG, CHEUO-FA-KI, LIOU-OUI-TAO, *Bl.* [5] 1 [1934] 1233; AKERMANN, *C. r.* 201 [1935] 210; URASOWSKI, SCHARASCHENIDSE, *Ukr. chemič. Ž.* 10 [1935] 152; *C.* 1936 I 3657; LOISY, *Bl.* [5] 5 [1938] 1509, 7 [1940] 698; SWIDEREK, *Roczniki Chem.* 18 [1938] 789; *C.* 1939 II 3030; BARDAN,

Chlorpikrin enthaltende azeotrope Gemische.

Komponente	Kp_{760} °	Chlorpikrin in Gew.-%	Seitenzahlen [1]	Komponente	Kp_{760} °	Chlorpikrin in Gew.-%	Seitenzahlen [1]
Nitromethan	<100,4	<15	328	tert.-Butylalkohol	82,25	37	104
Heptan	98,32	9	312	sek.-Amylalkohol	108,0	83	104
Diisobutyl	<107,5	<55	312	Diäthylcarbinol	<107,3	<82	104
Methylcyclohexan	100,8	27	312	Dimethyläthylcarbinol	98,9	65	104
1.3-Dimethyl-cyclohexan	111,0	80	312	Methylisopropylcarbinol	<106,5	<80	104
Äthylalkohol	77,5	24	104	Isobutylcarbinol	111,15	93,0	104
β-Chlor-äthylalkohol	108,9	85	137	Allylalkohol	94,2	56	104
Isopropylalkohol	81,95	35	104	Glykolmonomethyläther	<110,5	<82	150
1-Chlor-propanol-(2)	<111,6	<96	137	Essigsäure	107,65	80,5	24
Butylalkohol	106,65	80	104				
sek.-Butylalkohol	96,1	60	104				

[1]) Die angegebenen Seitenzahlen beziehen sich auf M. LECAT, Tables azéotropiques, 2. Aufl. [Brüssel 1949]. Vgl. a. L. H. HORSLEY, Azeotropic Data (= Advances in Chemistry Series 6) [Washington 1952] S. 268.

SCARLATESCU, *Bl.* [5] 6 [1939] 46; DUBININ, TIMOFEJEW, *C. r. Doklady* 54 [1946] 701; *C. A.* 1947 7198; DANBY, Mitarb., *Soc.* 1946 933; DOLE, KLOTZ, *Ind. eng. Chem.* 38 [1946] 1289; DOLE, *J. chem. Physics* 15 [1947] 447. Adsorption an Aluminium- und Eisenhydroxyd sowie Titandioxydgele: ALEXEJEWSKI, BELOZERKOWSKI, *Ž. obšč. Chim.* 6 [1936] 374. Beschleunigende Wirkung auf die Autoxydation von Tetralin: ROBERTSON, WATERS, *Soc.* 1947 494.

Chemisches Verhalten

Über die Zersetzung in Phosgen und Nitrosylchlorid (E II 42) im Sonnenlicht vgl. MOUREU, CHOVIN, TRUFFERT, *C. r.* 228 [1949] 1954. Kinetik der thermischen Zersetzung in Phosgen und Nitrosylchlorid bei 130—160°: RADULESCU, ZAMFIRESCU, *Bulet. Soc. chim. România* 17 [1935] 87; *C.* 1937 I 830; bei niedrigen Drucken: STEACIE, SMITH, *Canad. J. Res.* [B] 16 [1938] 222; *J. chem. Physics* 6 [1938] 145. Die thermische Zersetzung wird von Metallen nur in geringem Maß beschleunigt (PETROW, SSAWELJEW, *Ž. prikl. Chim.* 2 [1929] 629; *C.* 1930 I 2076). Liefert bei der Reduktion mit Zinnpulver und konz. HCl in Äther bei 0—5° Dichlorformaldoxim (Syst. Nr. 208) (GRYSZKIEWICZ-TROCHIMOWSKI, DYMOWSKI, SCHMIDT, *Bl.* 1948 597). Bei der elektrolytischen Reduktion entstehen je nach den Bedingungen wechselnde Mengen Trichlornitrosomethan (S. 105), N-Methyl-hydroxylamin, Methylamin und Dichlorformaldoxim (BRINTZINGER, ZIEGLER, SCHNEIDER, *Z. El. Ch.* 53 [1949] 110). Spaltet bei der Hydrolyse in wss. Lösung im Dunkeln innerhalb 38 Tagen das gesamte Chlor ab; die Hydrolyse wird durch Röntgenstrahlen und UV-Licht beschleunigt (ALEXEJEWSKI, *Ž. obšč. Chim.* 2 [1932] 343; *C.* 1933 I 3683). Gibt mit Kaliumbromid in Methanol Tetrabromkohlenstoff, Brompikrin, Chlordibromnitromethan, Nitromethan und andere Produkte (SSYTSCHEW, *Ž. chim. Promyšl.* 7 [1930] 1168; *C.* 1931 I 2188). Beim Kochen mit Kaliumjodid in Äthanol erhält man Tetrajodmethan, Kohlendioxyd, Kohlenoxyd und andere Produkte (KRETOW, MELNIKOW, *Ž. obšč. Chim.* 2 203, 207; vgl. Ss.). Zersetzung mit Natriumhydrosulfid oder Kaliumsulfid: KR., ME., *Ž. obšč. Chim.* 2 [1932] 203, 204. Das Chlor wird beim Kochen mit Natriumsulfid und Äthanol abgespalten (KR., PANTSCHENKO, SSAWITSCH, *Ž. obšč. Chim.* 1 [1931] 421). Zeigt bei der Reaktion mit Phenylmagnesiumbromid in Äther grüne Luminescenz (WEDEKIND, *Phys. Z.* 7 [1906] 805; vgl. a. E II 42); Luminescenzerscheinungen mit anderen Organomagnesiumverbindungen: DUFFORD, CALVERT, NIGHTINGALE, *Am. Soc.* 45 [1923] 2069, 2071; GILMAN, MCGLUMPHY, FOTHERGILL, *R.* 49 [1930] 530.

E II 42, Z. 22 v. u. statt „Pararosolsäure" lies „Aurin (?)".

Physiologisches Verhalten; Verwendung; Analytisches

Hemmende Wirkung auf verschiedene Dehydrogenasen: MACKWORTH, *Biochem. J.* 42 [1948] 82. Wirkung auf Bodenbakterien: BERESOWA, KULIKOWA, TRJASSUNOWA, *Mikrobiologija* 6 [1937] 773; *C.* 1938 I 700; auf Milchbakterien: BERTRAND, LEMOIGNE, *C. r.* 220 [1945] 721; auf gärfähige Flüssigkeiten: BERTRAND, *C. r.* 219 [1944] 231. Giftwirkung auf Pflanzen: GODFREY, *Sci.* 77 [1933] 583; *C.* 1934 II 4013; BERTRAND; HEUSCHEM, FIRKET, BACQ, *Bl. Soc. Chim. biol.* 29 [1947] 453; *C. A.* 1948 253; DAVID, *C. r.* 228 [1949] 198. Zur Toxizität vgl. HEUBNER, *Z. ges. exp. Med.* 107 [1940] 749; *C. A.* 1943 1513. Wirkung auf Nahrungsmittel: MIHAILESCU, BALABAN, SCHÖBESCH, *Antigaz* 8 39; *C.* 1934 II 1718.

Verwendung zur Schädlingsbekämpfung: STRAND, *Ind. eng. Chem. Anal.* 2 6, 7; *C.* 1930 I 2471; JOHNSON, GODFREY, *Ind. eng. Chem.* 24 [1932] 310; LEHMAN, *J. econ. Entomol.* 26 [1933] 1042; *C.* 1934 I 1867; STONE, CAMPBELL, *J. econ. Entomol.* 26 233; *C.* 1933 I 3120; HARUKAWA, KUMASHIRO, *Ber. Ohara-Inst.* 6 [1934] 407; *C.* 1935 II 110; JOHNSON, *Soap* 11 [1935] Nr. 11 S. 105; *C.* 1936 I 2618; GOUNELLE, RAOUL, *C. r.* 203 [1936] 689; PETERS, *Z. ges. Getreidew.* 24 [1937] 205; *C.* 1938 I 704; STARK, *Mem. N. Y. State agric. Exp. Station* 278 [1948] 3; *C. A.* 1949 3960; vgl. a. D. E. H. FREAR, Chemistry of Insecticides, Fungicides and Herbicides, 2. Aufl. [New York 1948] S. 111, 317; H. H. SHEPARD, The Chemistry and Action of Insecticides [New York 1951] S. 251; A. W. A. BROWN, Insect Control by Chemicals [New York 1951]. Bibliographie über Chlorpikrin als Insektizid 1848—1932: ROARK, *U. S. Dep. Agric. Misc. Publ.* Nr. 176, *C.* 1934 II 1113; 1932—1934: RO., BUSBEY, *U. S. Dep. Agric., Bur. Entomol.* E-351 [1935]. Verwendung zur Steigerung der Ertragsfähigkeit des Bodens: BERESOWA, GORBUNOWA, KOSLOWA, *Chimis. sozialist. Seml.* 1935 Nr. 8, S. 59; *C.* 1936 I 2184; MISCHUSSTIN, *Mikrobiologija* 5 [1936] 194; *C.* 1937 I 2006; LICHATSCHEW, *Chimis. sozialist. Seml.* 6 [1937] Nr. 9, S. 87; *C.* 1938 I 2431; SCHTSCHEPETILNIKOWA, TSCHERMISSOWA, *Chimis. sozialist. Seml.* 6 [1937] Nr. 8, S. 39; *C.* 1938 I 2431; GUSSEINOW, *Chimis. sozialist. Seml.* 7 [1938] Nr. 8 9, S. 74; *C.* 1939 I 2056; TAM, *Soil Sci.* 59 191; *C. A.* 1945 2838. Verwendung zur Sterilisierung von Boden: BERTRAND, *C. r.* 219 [1944] 231. Verwendung zur Kenntlichmachung von Blausäure: DEGUSSA, D.R.P. 517631 [1925]; *Frdl.* 17 2180.

Nachweis durch das bei der thermischen Zersetzung (500°) gebildete Chlor: TSCHMUTOW, SHUKOW, *Ž. prikl. Chim.* 5 [1932] 425; *C.* 1933 I 2287; durch die Nitritbildung bei Einw. von Natriumäthylat-Lösung und die Farbreaktion des Nitrits mit Sulfanilamid: ALEXEJEWSKI, *Ž. chim. Promyšl.* 8 [1931] Nr. 20, S. 50; *C.* 1932 II 1208; FENTON, *J. chem. Educ.* 20 [1943] 564, 21 [1944] 488; *C. A.* 1944 898, 1945 135; durch die mit einer Mischung von Natriumcyanid und

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Frankfurt am Main

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(±)-Methylphosphonsäure-äthylester-[2-dimethylamino-äthylester] $C_7H_{18}NO_3P$, Formel I (R = CH_2-CH_2-$N(CH_3)_2$, R′ = C_2H_5).

B. Aus (±)-Methylphosphonsäure-äthylester-chlorid und 2-Dimethylamino-äthanol mit Hilfe von Triäthylamin (*Tammelin*, Acta chem. scand. **11** [1957] 1340, 1342).

$Kp_{0,05}$: 56°. D_4^{25}: 1,0294. n_D^{25}: 1,4320. Wahrer Dissoziationsexponent pK_a (H_2O; potentiometrisch ermittelt) bei 25°: 8,14 (*Ta.*, l. c. S. 1346).

Hydrogenoxalat $C_7H_{18}NO_3P \cdot C_2H_2O_4$. Kristalle (aus Acn.); F: 85° (*Ta.*, l. c. S. 1344).

(±)-[2-(Äthoxy-methyl-phosphinoyloxy)-äthyl]-trimethyl-ammonium $[C_8H_{21}NO_3P]^+$, Formel II.

Jodid $[C_8H_{21}NO_3P]I$. *B.* Aus der vorangehenden Verbindung und CH_3I (*Tammelin*, Acta chem. scand. **11** [1957] 1340, 1345). — F: 100° (*Ta.*, Acta chem. scand. **11** 1345). — Geschwindigkeitskonstante der Hydrolyse in wss. NaOH bei 25°: *Tammelin*, Ark. Kemi **12** [1958] 287, 291.

(±)-Methylphosphonsäure-[2-dimethylamino-äthylester]-isopropylester $C_8H_{20}NO_3P$, Formel I (R = CH_2-CH_2-$N(CH_3)_2$, R′ = $CH(CH_3)_2$).

B. Aus Methylphosphonsäure-chlorid-isopropylester und 2-Dimethylamino-äthanol mit Hilfe von Triäthylamin (*Tammelin*, Acta chem. scand. **11** [1957] 1340, 1342).

$Kp_{0,3}$: 70°. D_4^{25}: 0,9992. n_D^{25}: 1,4285. Wahrer Dissoziationsexponent pK_a (H_2O; potentiometrisch ermittelt) bei 25°: 8,24 (*Ta.*, l. c. S. 1346).

Hydrogenoxalat $C_8H_{20}NO_3P \cdot C_2H_2O_4$. Kristalle (aus Acn.); F: 100° (*Ta.*, l. c. S. 1344).

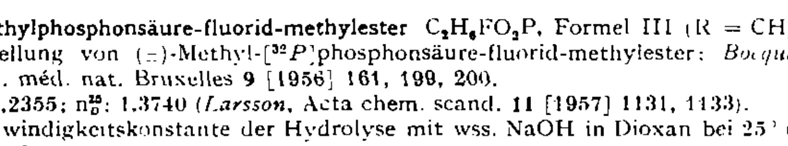
Methojodid $[C_9H_{23}NO_3P]I$; (±)-[2-(Isopropoxy-methyl-phosphinoyloxy)-äthyl]-trimethyl-ammonium-jodid. F: 114° (*Ta.*, l. c. S. 1345).

Methylphosphonsäure-bis-[2-dimethylamino-äthylester] $C_9H_{23}N_2O_3P$, Formel I (R = R′ = CH_2-CH_2-$N(CH_3)_2$).

B. Aus Methylphosphonsäure-dichlorid und Natrium-[2-dimethylamino-äthylat] (*Fan.*, Bl. **1957** 783, 785).

$Kp_{0,05}$: 78—80°. n_D^{25}: 1,4450.

Bis-metho-[toluol-4-sulfonat] $[C_{11}H_{29}N_2O_3P](C_7H_7SO_3)_2$; Methylphosphonsäure-bis-[2-trimethylammonio-äthylester]-bis-[toluol-4-sulfonat]. F: 120—122° [geschlossene Kapillare].



I II III

Methylphosphonsäure-monofluorid CH_4FO_2P, Formel III (R = H).

Bildung bei mehrjährigem Aufbewahren von (±)-Methylphosphonsäure-fluorid-isopropylester: *Lorquet, Vassart*, Bl. Soc. chim. Belg. **68** [1959] 336, 341.

IR-Spektrum (CS_2 bzw. CCl_4; 1500—700 cm^{-1}): *Lo., Va.*

(±)-Methylphosphonsäure-fluorid-methylester $C_2H_6FO_2P$, Formel III (R = CH_3).

Herstellung von (±)-Methyl-[^{32}P]phosphonsäure-fluorid-methylester: *Bocquet*, Ann. Soc. Sci. méd. nat. Bruxelles **9** [1956] 161, 199, 200.

D_4^{25}: 1,2355; n_D^{25}: 1,3740 (*Larsson*, Acta chem. scand. **11** [1957] 1131, 1133).

Geschwindigkeitskonstante der Hydrolyse mit wss. NaOH in Dioxan bei 25° und 35°: *La.*, l. c. S. 1138.

(±)-Methylphosphonsäure-äthylester-fluorid $C_3H_8FO_2P$, Formel III (R = C_2H_5).

Herstellung von (±)-Methyl-[^{32}P]phosphonsäure-äthylester-fluorid: *Bocquet*, Ann. Soc. Sci. méd. nat. Bruxelles **9** [1956] 161, 202.

D_4^{25}: 1,5124; n_D^{25}: 1,3785 (*Larsson*, Acta chem. scand. **11** [1957] 1131, 1133).

Geschwindigkeitskonstante der Hydrolyse mit wss. NaOH in Dioxan bei 25° und 35°: *La.*, l. c. S. 1138.

(±)-Methylphosphonsaure-[3,3-dimethyl-butylester]-fluorid $C_7H_{16}FO_2P$, Formel III (R = CH_2-CH_2-$C(CH_3)_3$) auf S. 3506.

B. Aus (±)-Methylphosphonsäure-chlorid-fluorid und 3,3-Dimethyl-butan-1-ol (*Larsson*, Acta chem. scand. **11** [1957] 1131, 1132, 1133).

$Kp_{0,5}$: 50°. D_4^{25}: 1,0211. n_D^{25}: 1,4055.

Geschwindigkeitskonstante der Hydrolyse in wss. Dioxan vom pH 8,5 bei 25° und 35°: *La.*, l. c. S. 1138.

(±)-Methylphosphonsäure-[2-dimethylamino-äthylester]-fluorid $C_5H_{13}FNO_2P$, Formel III (R = CH_2-CH_2-$N(CH_3)_2$) auf S. 3506.

B. Aus (±)-Methylphosphonsäure-chlorid-fluorid und 2-Dimethylamino-äthanol mit Hilfe von Triäthylamin (*Tammelin*, Acta chem. scand. **11** [1957] 859, 860, 861).

$Kp_{0,2}$: 40°; D_4^{25}: 1,14; n_D^{25}: 1,4130 (*Ta.*).

Methojodid [$C_6H_{16}FNO_2P$]I; (±)-[2-(Fluor-methyl-phosphinoyloxy)-äthyl]-trimethyl-ammonium-jodid. Geschwindigkeitskonstante der Hydrolyse in wss. Äthanol vom pH 8,5 bei 25° sowie vom pH 8 bei 35°: *Larsson*, Acta chem. scand. **11** [1957] 1131, 1138, 1141.

(±)-[3-(Fluor-methyl-phosphinoyloxy)-propyl]-trimethyl-ammonium [$C_7H_{18}FNO_2P$]⁺, Formel III (R = $[CH_2]_3$-$N(CH_3)_3^+$) auf S. 3506.

Jodid [$C_7H_{18}FNO_2P$]I. *B.* Beim Erwärmen von (±)-Methylphosphonsäure-chlorid-fluorid mit 3-Dimethylamino-propan-1-ol und Triäthylamin und anschliessenden Behandeln mit CH_3I (*Tammelin*, Ark. Kemi **12** [1958] 287, 288). — F: 82° (*Ta.*). — Geschwindigkeitskonstante der Hydrolyse in wss. Äthanol vom pH 8,5 bei 25° und 35°: *Larsson*, Acta chem. scand. **11** [1957] 1131, 1138, 1141.

***Opt.-inakt. Methylphosphonsaure-[β-dimethylamino-isopropylester]-fluorid** $C_6H_{15}FNO_2P$, Formel III (R = $CH(CH_3)$-CH_2-$N(CH_3)_2$) auf S. 3506.

B. Aus (±)-Methylphosphonsaure-chlorid-fluorid und (±)-1-Dimethylamino-propan-2-ol mit Hilfe von Triäthylamin (*Tammelin*, Acta chem. scand. **11** [1957] 859, 860, 861).

$Kp_{0,1}$: 40°. D_{4}^{25}: 1,06. n_D^{25}: 1,4150

***Opt.-inakt. [2-(Fluor-methyl-phosphinoyloxy)-propyl]-trimethyl-ammonium** [$C_7H_{18}FNO_2P$]⁺, Formel III (R = $CH(CH_3)$-CH_2-$N(CH_3)_3^+$) auf S. 3506.

Jodid [$C_7H_{18}FNO_2P$]I. *B.* Aus der vorangehenden Verbindung und CH_3I (*Tammelin*, Acta chem. scand. **11** [1957] 859, 862). — F: 84° (*Ta.*). — Geschwindigkeitskonstanten der Hydrolyse in wss. Äthanol vom pH 8,5 bei 25° und 35°: *Larsson*, Acta chem. scand. **11** [1957] 1131, 1138, 1141.

Methylphosphonsäure-difluorid CH_3F_2OP = CH_3-POF_2.

B. Beim Leiten von HF in eine Schmelze von Methylphosphonsäure-dichlorid (*Dawson*, *Kennard*, J. org. Chem. **22** [1957] 1671). Beim Behandeln der Verbindung von Trichlor-methyl-phosphonium-chlorid mit $AlCl_3$ mit HF und anschliessend mit SO_2 (*Coates, Carter*, U.S.P. 2835515 [1952]). Beim Erhitzen von PF_3 mit Dimethyläther oder Methylacetat in Gegenwart von $AlCl_3$ auf 250° (*Kellogg Co.*, U.S.P. 2882315 [1954]).

Kp: 98–99°; D_4^{25}: 1,3609; n_D^{25}: 1,3148 (*Da.*, *Ke.*). Kp_{27}: 22°; D_4^{20}: 1,3838; n_D^{20}: 1,3277 (*Rusumow et al.*, Ž. obšč. Chim. **28** [1958] 194, 196; engl. Ausg. S. 194, 196). ³¹P-NMR-Absorption: *Finegold*, Ann. N.Y. Acad. Sci. **70** [1957] 875, 884.

Tetrafluor-methyl-phosphoran CH_3F_4P = CH_3-PF_4.

B. Aus der Verbindung von Trichlor-methyl-phosphonium-chlorid mit $AlCl_3$ und HF (*Coates, Carter*, U.S.P. 2853515 [1952]). Beim Aufbewahren von Difluor-methyl-phosphin (*Kulakowa et al.*, Ž. obšč. Chim. **29** [1959] 3957; engl. Ausg. S. 3916).

Kp: 9° (*Ku. et al.*).

(±)-Methylphosphonsäure-chlorid-methylester $C_2H_6ClO_2P$, Formel IV (R = CH_3) auf S. 3511.

B. Aus Methylphosphonsäure-dichlorid und Methanol mit Hilfe von Triäthylamin (*de Roos*, R. **78** [1959] 145, 146).

Kp_4: 39°; n_D^{20}: 1,4351 (*de Roos*).

Verbindung mit Aluminiumchlorid $C_2H_6ClO_2P \cdot AlCl_3$. *B.* Aus der Verbindung von Trichlor-methyl-phosphonium-chlorid mit $AlCl_3$ und Methanol (*Hoffmann et al.*, Am. Soc. **79** [1957] 3570, 3575). — Kristalle [aus CH_2Cl_2] (*Ho. et al.*).

(±)-Methylphosphonsäure-äthylester-chlorid $C_3H_8ClO_2P$, Formel IV ($R = C_2H_5$) auf S. 3511.

B. Aus Methylphosphonsäure-dichlorid und Äthanol mit Hilfe von Triäthylamin (*Hudson, Keay*, Soc. **1956** 2463, 2466; *de Roos*, R. **78** [1959] 145, 146). Aus Methylphosphonsäure-diäthylester und $COCl_2$ (*Coe et al.*, Soc. **1957** 3604, 3606). Beim Behandeln der Verbindung von Trichlor-methyl-phosphonium-chlorid mit $AlCl_3$ mit Äthanol und anschliessend mit H_2O (*Hoffmann et al.*, Am. Soc. **79** [1957] 3570, 3574).

Kp_5: 64° (*Hu., Keay*); $Kp_{3,5}$: 49–49,5° (*de Roos*); Kp_1: 40–41° (*Hu., Keay*); $Kp_{0,9}$: 33° (*Ho. et al.*); $Kp_{0,7}$: 37° (*Coe et al.*). n_D^{20}: 1,4345 (*de Roos*); n_D^{25}: 1,4320 (*Coe et al.*; *Ho. et al.*). ^{31}P-NMR-Absorption: *Finegold*, Ann. N.Y. Acad. Sci. **70** [1957] 875, 884.

(±)-Methylphosphonsäure-[2-chlor-äthylester]-chlorid $C_3H_7Cl_2O_2P$, Formel IV ($R = CH_2\text{-}CH_2Cl$) auf S. 3511.

B. Neben Methylphosphonsäure-dichlorid beim Erhitzen von Methylphosphonsäure-bis-[2-chlor-äthylester] mit PCl_5 unter vermindertem Druck (*Gefter, Kabatschnik*, Izv. Akad. S.S.S.R. Otd. chim. **1957** 194, 195, 197; engl. Ausg. S. 205, 206, 207).

Kp_3: 92–93°. D_4^{20}: 1,3862. n_D^{20}: 1,4658.

(±)-Methylphosphonsäure-chlorid-propylester $C_4H_{10}ClO_2P$, Formel IV ($R = CH_2\text{-}CH_2\text{-}CH_3$) auf S. 3511.

B. Aus Methylphosphonsäure-dichlorid und Propan-1-ol mit Hilfe von Triäthylamin (*de Roos*, R. **78** [1959] 145, 146). Beim Behandeln der Verbindung von Trichlor-methyl-phosphonium-chlorid mit $AlCl_3$ mit Propan-1-ol und anschliessend mit H_2O (*Hoffmann et al.*, Am. Soc. **79** [1957] 3570, 3574). Aus Methylphosphonsäure-dipropylester und $COCl_2$ (*Coe et al.*, J. org. Chem. **24** [1959] 1018).

Kp_2: 43–45°; n_D^{20}: 1,4353 (*de Roos*). Kp_1: 46°; n_D^{25}: 1,4332 (*Ho. et al.*). ^{31}P-NMR-Absorption: *Finegold*, Ann. N.Y. Acad. Sci. **70** [1957] 875, 884.

(±)-Methylphosphonsäure-chlorid-isopropylester $C_4H_{10}ClO_2P$, Formel IV ($R = CH(CH_3)_2$) auf S. 3511. Chlorosar

B. Aus Methylphosphonsäure-dichlorid und Isopropylalkohol (*Larsson*, Acta chem. scand. **12** [1958] 303, 305). Aus Methylphosphonsäure-diisopropylester und $COCl_2$ (*Coe et al.*, Soc. **1957** 3604, 3606; *de Roos, Toet*, R. **78** [1959] 59, 62, 65; *Rasumow et al.*, Ž. obšč. Chim. **27** [1957] 2389, 2390, 2392; engl. Ausg. S. 2450, 2453).

Kp_4: 51°; D_4^{25}: 1,140; n_D^{25}: 1,4275 (*La.*). Kp_2: 49,1–49,3°; n_D^{20}: 1,4301 (*de Roos, Toet*). Kp_1: 40°; n_D^{25}: 1,4285 (*Coe et al.*). $Kp_{0,5}$: 36–37°; D_4^{20}: 1,2924; n_D^{20}: 1,4346 (*Ra. et al.*).

Geschwindigkeitskonstante der Hydrolyse in wss. Lösung vom pH 7,0 bei 25°: *La.*, l. c. S. 306. Enthalpie der Hydrolyse in H_2O bei 22–23°: *Neale, Williams*, Soc. **1955** 2485, 2487; in wss. NaOH bei 25°: *Larsson, Bergner*, Ark. Kemi **13** [1959] 143, 146.

(±)-Methylphosphonsäure-butylester-chlorid $C_5H_{12}ClO_2P$, Formel IV ($R = [CH_2]_3\text{-}CH_3$) auf S. 3511.

B. Aus Methylphosphonsäure-dichlorid und Butan-1-ol (*Andrianow, Nowikowa*, Vysokomol. Soedin. **1** [1959] 1390, 1393; C. A. **1960** 20851; *de Roos*, R. **78** [1959] 145, 146).

Kp_9: 78–79° (*An., No.*). $Kp_{0,8}$: 59°; n_D^{20}: 1,4382 (*de Roos*).

(±)-Methylphosphonsäure-chlorid-pentylester $C_6H_{14}ClO_2P$, Formel IV ($R = [CH_2]_4\text{-}CH_3$) auf S. 3511.

B. Aus Methylphosphonsäure-dichlorid und Pentan-1-ol mit Hilfe von Triäthylamin (*de Roos*, R. **78** [1959] 145, 147).

Kp_2: 60–61°; $Kp_{0,8}$: 59°. n_D^{20}: 1,4415.

Methylphosphonsäure-dichlorid $CH_3Cl_2OP = CH_3\text{-}POCl_2$.

B. Beim Erhitzen von PCl_3 mit Formaldehyd-dimethylacetal in Gegenwart von NiI_2 auf 250° (*Kellogg Co.*, U.S.P. 2882305 [1953], 2882310 [1954]). Aus Methylphosphonsäure-dimethylester und PCl_5 (*Crofts, Kosolapoff*, Am. Soc. **75** [1953] 3379, 3380). Beim Erhitzen von Methylphosphonsäure-diisopropylester mit $SOCl_2$ (*Dawson, Armstrong*, Beilstein, F[illegible]

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1-[4-Chlor-phenyl]-äthanon-(1) (*Hollıman, Mann*, Soc. **1945** 37, 43; *Temnikowa, Kulischkowa*, Ž. obšč. Chim. **19** [1949] 1324, 1339; C. A. **1950** 4442).

F: 204–206° (*Ho., Mann*), 202–204° (*Lau., Sp.*), 192–194° (*Te., Ku.*).

[1-(4-Chlor-phenyl)-äthyliden]-[(2.4-dichlor-phenoxy)-acetyl]-hydrazin, [2.4-Dichlor-phenoxy]-essigsäure-[1-(4-chlor-phenyl)-äthylidenhydrazid], *(2,4-dichlorophenoxy)-acetic acid (4-chloro-α-methylbenzylidene)hydrazide* $C_{16}H_{13}Cl_3N_2O_2$, Formel XIII.

B. Durch Kochen von 1-[4-Chlor-phenyl]-äthanon-(1) mit [2.4-Dichlor-phenoxy]-essigsäure-hydrazid in Äthanol (*Chao, Sah, Oneto*, R. **68** [1949] 506, 507).

Krystalle (aus A.); F: 165–166° [unkorr.].

Chloracetyl-benzol, 2-Chlor-1-phenyl-äthanon-(1), Phenacylchlorid, ω-Chlor-acetophenon, *2-chloroacetophenone* C_8H_7ClO, Formel XIV (H 282; E I 151; E II 219).

B. Durch Behandeln von Benzol mit 0.25 Mol Chloracetylchlorid und 0,25 Mol $AlCl_3$ (*Levin, Hartung*, Org. Synth. Coll. Vol. III [1955] 191, 192; vgl. H 282). Durch Erwärmen von (±)-2-Chlor-1-phenyl-äthanol-(1) mit $Na_2Cr_2O_7$ und wss. H_2SO_4 auf 60° (*Hanby, Rydon*, Soc. **1946** 114). Durch Einleiten von Chlor in eine Lösung von Acetophenon in wss. HCl und Essigsäure unter Kühlung (*Isacescu*, Bulet. [2] 3 [1941/42] 182, 184; vgl. H 282). Durch Elektrolyse einer Lösung von Acetophenon in wss. HCl und Essigsäure unter Verwendung von Graphit-Elektroden (*Szper*, Bl. [4] **51** [1932] 653, 655). Durch Erwärmen von Acetophenon mit $NaClO_3$ und wss. HCl auf 70° (*Riedel-de Haën*, Cios Rep. XXVII 81 [1945]; Brit. Abstr. **1948** B I 132).

Krystalle (aus A. oder CCl_4) (*Mohler, Pólya*, Helv. **19** [1936] 1222, 1238; *Mohler, Sorge*, Helv. **21** [1938] 67, 70; *Rheinboldt, Perrier*, Univ. São Paulo Fac. Fil. Química Nr. 2 [1947] 110, 114). F: 58,8° (*Mo., So.*, Helv. **21** 70), 56,5–56,8° (*Kohlrausch, Pongratz*, M. **64** [1934] 374, 379). Kp_{10}: 120.0–120.2° (*Ko., Po.*). Dampfdruck bei Temperaturen von 10° (0.00107 Torr) bis 50° (0,128 Torr): *Balson*, Trans. Faraday Soc. **43** [1947] 54, 59. Raman-Spektrum: *Ko., Po.* UV-Spektrum (Hexan): *Mohler, Pólya*, Helv. **19** [1936] 1222, 1225, 1239, 1241; *Mohler, Sorge*, Helv. **23** [1940] 100, 101, 104, 108. Dipolmoment (ε; Bzl.): 3.26 D (*Mo., So.*, Helv. **21** 70). Assoziation in flüssigem SO_2: *Jander, Mesech*, Z. physik. Chem. [A] **183** [1939] 277, 289. Schmelzdiagramme der binären Systeme mit Tetrachlormethan (Mischkrystallbildung), Benzol (Eutektikum), Äthanol (Mischkrystallbildung) und Acetophenon (Eutektikum): *Kireew, Kaplan, Wašnewa*, Ž. fiz. Chim. **5** [1934] 739, 740; C. **1935** II 2043; mit 2-Brom-1-phenyl-äthanon-(1) (Mischkrystallbildung) und mit 2-Jod-1-phenyl-äthanon-(1) (Eutektikum): *Rh., Pe.*, l. c. S. 111, 114, 117; mit 10-Chlor-9a.10-dihydro-phenarsazin (Eutektikum): *Pusin, Hrustanovic*, B. **71** [1938] 798, 800.

Beim Kochen mit 2,6 Mol Brom in Essigsäure unter Zusatz von Natriumacetat werden 2.2.2-Tribrom-1-phenyl-äthanon-(1) (Hauptprodukt) und 2-Chlor-2.2-dibrom-1-phenyl-äthanon-(1) (ω-Chlor-ω.ω-dibrom-acetophenon; nicht näher beschrieben) erhalten (*Aston et al.*, Am. Soc. **64** [1942] 1413, 1415). Geschwindigkeit der Reaktion mit Brom in 90%ig. wss. Essigsäure in Gegenwart von HCl bei 25°: *Nathan, Watson*, Soc. **1933** 890, 893. Beim Behandeln mit 0,5 Mol $SeOCl_2$ in Äther entsteht Dichlor-bis-[4-chlor-phenacyl]-selen (*Nelson, Jones*, Am. Soc. **52** [1930] 1588). Beim aufeinanderfolgenden Einleiten von HCl und H_2S in eine äthanol. Lösung unter Kühlung bildet sich 2.5-Diphenyl-[1.4]dithiin (*Böhme, Pfeifer, Schneider*, B. **75** [1942] 900, 905, 908). Beim Behandeln mit einem Gemisch von Salpetersäure (D: 1,5) und konz. Schwefelsäure unterhalb –20° sind 2-Chlor-1-[3-nitro-phenyl]-äthanon-(1) (Hauptprodukt) sowie geringere Mengen eines Gemisches von 2-Chlor-1-[2-nitro-phenyl]-äthanon-(1), 2-Chlor-1-[4-nitro-phenyl]-äthanon-(1) und Benzoesäure erhalten worden (*Barkenbus, Clements*, Am. Soc. **56** [1934] 1369; vgl. E II 219). Beim 20-stdg. Kochen mit Wasser entsteht 2-Hydroxy-1-phenyl-äthanon-(1) (*Weidenhagen, Herrmann*, B. **68** [1935] 1953, 1955 Anm. 9). Geschwindigkeit der Hydrolyse in Wasser bei 30°: *Edwards, Evans, Watson*, Soc. **1937** 1942, 1946.

Beim Behandeln einer auf 60° erwärmten äthanol. Lösung mit wss.-äthanol. KOH bildet sich 1.4-Diphenyl-buten-(2)-dion-(1.4) (F: 128–134°) (*Bogoslowškii*, Ž. obšč. Chim. **14** [1944] 993; C. A. **1945** 4600). Die beim Behandeln mit äthanol. Natriumäthylat-Lösung erhaltenen, als α-Chlordiphenacyl und β-Chlordiphenacyl bezeichneten Verbindungen (H 7 282; s. a. E II 7 219; H 19 54; E I 19 623; E II 19 44) sind

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Frankfurt am Main

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***[1-(4-Chlor-phenyl)-äthyliden]-carbazidsäure-[2-hydroxy-äthylester]** $C_{11}H_{13}ClN_2O_3$, Formel XIII (R = CO-O-CH_2-CH_2-OH).

B. Aus 1-[4-Chlor-phenyl]-äthanon und Carbazidsäure-[2-hydroxy-äthylester] in Äthanol (*Eloy, Moussebois*, Bl. Soc. chim. Belg. **68** [1959] 423, 427, 428).

Kristalle (aus wss. A.); F: 115°.

Allophansäure-[1-(4-chlor-phenyl)-äthylidenhydrazid], 1-[4-Chlor-phenyl]-äthanon-allophanoylhydrazon $C_{10}H_{11}ClN_4O_2$, Formel XIII (R = CO-NH-CO-NH_2).

B. Aus Allophansäure-hydrazid und 1-[4-Chlor-phenyl]-äthanon (*Audrieth, Gordon*, J. org. Chem. **20** [1955] 244, 246).

Kristalle (aus A.); F: 216°.

***1-[4-Chlor-phenyl]-äthanon-[4-isobutyl-thiosemicarbazon]** $C_{13}H_{18}ClN_3S$, Formel XIII (R = CS-NH-CH_2-$CH(CH_3)_2$).

B. Aus 1-[4-Chlor-phenyl]-äthanon und 4-Isobutyl-thiosemicarbazid in wss. Äthanol (*Dodgen, Nobles*, J. Am. pharm. Assoc. **46** [1957] 437).

Kristalle (aus wss. A.), F: 125–126° [unkorr.].

***[1-(4-Chlor-phenyl)-äthyliden]-hydrazidophosphorsäure-diphenylester** $C_{20}H_{18}ClN_2O_3P$, Formel XIII (R = $PO(OC_6H_5)_2$).

B. Aus 1-[4-Chlor-phenyl]-äthanon und Hydrazidophosphorsäure-diphenylester in Äthanol (*Audrieth et al.*, J. org. Chem. **20** [1955] 1288, 1290).

Kristalle (aus A.); F: 127° [unkorr.].

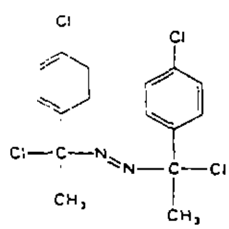
meso-**Bis-[1-chlor-1-(4-chlor-phenyl)-äthyl]-*trans*-diazen** $C_{16}H_{14}Cl_4N_2$, Formel I.

Konfiguration: *Levi, Malament*, J.C.S. Perkin II **1976** 1249, 1254.

B. Aus {(*E,E*)-Bis-[1-(4-chlor-phenyl)-äthyliden]}-hydrazin und Chlor (*Goldschmidt, Acksteiner*, A. **618** [1958] 173, 174, 180).

Kristalle (aus Acn.); F: 123° [Zers.] (*Go., Ack.*).

Geschwindigkeitskonstante des Zerfalls in Toluol bei 59° und 69° (Bildung von 2,3-Dichlor-2,3-bis-[4-chlor-phenyl]-butan [E IV 5 1941]): *Go., Ack.*



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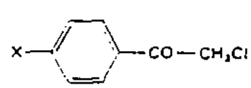
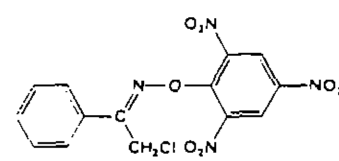


II



III

2-Chlor-1-phenyl-äthanon, Phenacylchlorid C_8H_7ClO, Formel II (X = H) (H 282; E I 151; E II 219; E III 967 [1]).

B. Beim Behandeln von Benzol mit Tetrakis-chloracetoxy-silan und $AlCl_3$ (*Jur'ew et al.*, Ž. obšč. Chim. **28** [1958] 2372, 2374; engl. Ausg. S. 2408).

Dipolmoment: 3,28 D [ε; CCl_4], 3,43 D [ε; Heptan] (*Nakagawa*, J. chem. Soc. Japan Pure Chem. Sect. **79** [1958] 1358, 1359, 1360; C. A. **1959** 7698).

Kristalle (aus A.), F: 57–57,5°; Kp_5: 101,5–102,5° (*Ju. et al.*). Frequenz und Intensität der CO-Valenzschwingungsbande: *Jones, Spinner*, Canad. J. Chem. **36** [1958] 1020, 1021, 1025; *Josien, Castinel*, Bl. **1958** 801, 802, s. a. *Bellamy et al.*, Soc. **1956** 3704; *Bellamy, Williams*,

[1] Berichtigung zu E III 7 968, Zeile 1–2 v. o.: Anstelle von „2r-Chlormethyl-2-phenyl-3t-benzoyl-oxiran bzw. 2r-Chlormethyl-2-phenyl-3c-benzoyl-oxiran" ist zu setzen „2r-Chlormethyl-2-phenyl-3c-benzoyl-oxiran bzw. 2r-Chlormethyl-2-phenyl-3t-benzoyl-oxiran".

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BENTLEY ET AL.

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ACUTE TOXICITY OF DIISOPROPYLMETHYL PHOSPHONATE AND DICYCLOPENTADIENE TO AQUATIC ORGANISMS

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ACUTE TOXICITY OF DIISOPROPYLMETHYL PHOSPHONATE AND DICYCLOPENTADIENE TO AQUATIC ORGANISMS

BY

R.E. BENTLEY, G.A. LEBLANC, T.A. HOLLISTER, AND B.H. SLEIGHT, III

FINAL REPORT

JULY, 1976

SUPPORTED BY

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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Fort Detrick, Frederick, Maryland 21701

CRITERIA FORMULATION

DIMP

The acute toxicity (LC50 and EC50) of diisopropylmethyl phosphonate to a wide variety of aquatic organisms representing several trophic forms (including primary producer organisms, primary consumers, and secondary consumers) under a wide variety of water quality conditions ranged from 257-6,332 mg/ℓ.

In lieu of a specific laboratory-derived application factor based on chronic toxicity studies, an appropriate application factor (e.g., 0.1, 0.05, 0.01) must be utilized to estimate safe concentrations during chronic exposure. The selection of an appropriate application factor must consider persistence, cumulative toxic effects, and bioaccumulation potential of the chemical. Acute toxicity studies with bluegill and aged solutions of DIMP indicate that after only 96 hours, acute toxicity of DIMP in water is less than 1/3-1/2 of that observed with fresh solutions suggesting a lack of persistence of DIMP in water. During continuous exposure of bluegill to 150 mg/ℓ DIMP for 14 days, no toxic effects were evident, indicating a lack of cumulative toxicity associated with this chemical. Finally, a pilot bioconcentration study with ^{14}C-DIMP demonstrated no bioaccumulation of the chemical by bluegill.

Based on these observations, it would appear that, in lieu of adequate chronic toxicity data, 0.05 probably represents a reasonable application factor for estimating safe concentrations of DIMP in water.

Based on an application factor of 0.05, and an LC50 of 257 mg/ℓ observed for the most sensitive aquatic organisms tested (bluegill, at 25°C), a water quality criterion of 12.5 mg/ℓ DIMP is recommended for the protection of freshwater aquatic life.

DCPD

The acute toxicity (LC50 and EC50) of dicyclopentadiene to a wide variety of aquatic organisms representing several trophic forms (including primary producer organisms, primary consumers and secondary consumers), under a wide variety of water quality conditions ranged from 10.5-120 mg/ℓ.

In lieu of a specific laboratory-derived application factor based on chronic toxicity studies, an appropriate application factor must be utilized to estimate safe concentrations during chronic exposure. Acute toxicity studies with bluegill indicate that the toxicity of DCPD solutions after 96 hours of aging is somewhat less than that of the fresh solutions. During continuous exposure of bluegill for 14 days to approximately

438 mg/ℓ, while those for the 100 mg/ℓ and 250 mg/ℓ hard water were 849 mg/ℓ and >1,000 mg/ℓ, respectively. Increased pH (8.0) appeared to reduce the toxicity of DIMP to comparable levels (96-hour LC50, >750<1,000).

Dissolved oxygen levels monitored during Task 4 (Stability of Toxicological Properties) appeared to remain constant throughout the "aging" periods, and decreased normally after introduction of the test organisms from 8.8 mg/ℓ (98% of saturation) to 2.8 mg/ℓ (31% of saturation) indicating that DIMP did not generate any significant oxygen demand. The pH values ranged from 6.9 to 7.5. In general, the data indicate that solutions of DIMP "aged" for 96 hours are approximately half as toxic to bluegill as unaged solutions (Tables 22 and 23) after 96 hours of exposure, while those solutions "aged" for shorter periods (0, 8. 24 and 48 hours of exposure) appeared as toxic at 96 hours of exposure as observed for bluegill in the other bioassays.

Those bluegill in Task 5 (Bioconcentration) exposed to 150 mg/ℓ ^{14}C-DIMP appeared normal, fed readily, and generally showed no signs of stress due to chemical toxicity. The mean measured concentration of ^{14}C-DIMP in the water through 14 days of exposure was 166.7 $\pm$ 13.6 mg/ℓ (nominal concentration 150.0 mg/ℓ).

The results of the analyses of edible portions of bluegill sampled during the 14 days of exposure are summarized in Table 24. Radiometric analyses indicate that the mean measured concentration of ^{14}C-residues remains below minimum detectable limits (100 mg/kg) throughout the entire observation period, and clearly indicates that bioconcentration of DIMP by bluegill does not occur.

Dicyclopentadiene (DCPD)

A summary of those calculated EC50 and LC50 values and 95% confidence limits at termination of exposure is presented (Table 25). Based on *in vivo* chlorophyll *a* reduction, the 96-hour EC50's for *M. aeruginosa*, *A. flos-aquae*, and *N. pelliculosa* were 31, 60 and 51 mg/ℓ , respectively. The 96-hour EC50 for *S. capricornutum* was >1,000 mg/ℓ, the highest concentration at which DCPD could be maintained in solution (Table 26).

The 96-hour EC50 values based on reduction of cell numbers of *M. aeruginosa*, *A. flos-aquae*, and *N. pelliculosa* were 31, 22 and 53 mg/ℓ , respectively, with the value for *S. capricornutum* again >100 mg/ℓ (Table 27).

At most test concentrations, DCPD produced a decrease in both chlorophyll *a* and cell numbers of exposed *M. aeruginosa* and *N. pelliculosa*. Both cell numbers and chlorophyll *a* content for *A. flos-aquae* and *S. capricornutum* appeared to be stimu-

Table 3 -- Continued.

Species	Calculated EC50 and LC50 values (mg active ingredient/ℓ)
Fish/Life Stages	144-hour LC50
Pimephales promelas/ eggs[g]	475(285-793)
	96-hour LC50
Pimephales promelas/ 1-hour fry[g]	>1,000
Pimephales promelas/ 7-day fry[g]	>1,000
Pimephales promelas/ 30-day fry[g]	635(524-769)
Pimephales promelas/ 60-day fry[g]	641(548-749)
Fish/Water Quality	96-hour LC50
Lepomis macrochirus/ 15°C	464(381-565)
Lepomis macrochirus/ 20°C	481(394-588)
Lepomis macrochirus/ 25°C	257(202-328)
Lepomis macrochirus/ 35 mg/ℓ hardness	438(361-532)
Lepomis macrochirus/ 100 mg/ℓ hardness	849(727-993)
Lepomis macrochirus/ 250 mg/ℓ hardness	>1,000
Lepomis macrochirus/ pH 6.0	527(441-631)

Table 24 -- Mean[a] concentrations of ^{14}C-diisopropylmethyl phosphonate[b] (DIMP, lot #2) measured in water and bluegill[c] (*Lepomis macrochirus*) during a 14-day exposure period and in bluegill during an additional 7-day depuration period following transfer of fish to flowing, ^{14}C-DIMP-free water.

	Day	Mean measured ^{14}C-residue concentration water (mg/ℓ)	bluegill (mg/kg)
Exposure	0	177.67	<100
	1	177.00	<100
	2	176.50	<100
	4	168.50	<100
	7	172.00	<100
	10	150.00	<100
	14	145.00	<100
		$\bar{x}$ = 166.67 (13.57)[d]	
Depuration	1		<100
	3		<100
	7		<100

[a] Mean based on two radiometric analyses for water and three radiometric analyses for fish.

[b] Minimum detectable limits = 7.5 mg/ℓ for water and 100 mg/kg for fish.

[c] Mean weight of bluegill was 3.0 g.

[d] Standard deviation (±).

LITERATURE REVIEW – PROBLEM DEFINITION STUDIES ON SELECTED CHEMICALS

FINAL REPORT

VOLUME II

CHEMISTRY, TOXICOLOGY AND POTENTIAL ENVIRONMENTAL EFFECTS OF SELECTED ORGANIC POLLUTANTS

by

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June 1978

Supported by

U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-77-C-7037

Arthur D. Little, Inc.
Cambridge, Massachusetts 02140

Prepared for the U.S. Army Toxic and Hazardous Materials Agency
under the Direction of the
U.S. Army Medical Bioengineering Research and Development Laboratory
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AD A186562

TECHNICAL REPORT 8610

DRINKING WATER CRITERIA FOR THE GROUNDWATER POLLUTANT
DIISOPROPYL METHYLPHOSPHONATE (DIMP)

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Prepared for

US Army Toxic and Hazardous Materials Agency

by

U S ARMY BIOMEDICAL RESEARCH & DEVELOPMENT LABORATORY
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July 1987

Approved for public release;
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U S ARMY MEDICAL RESEARCH & DEVELOPMENT COMMAND
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TABLE 1. SUMMARY OF ACUTE TOXICITY OF DIMP IN VARIOUS MAMMALIAN SPECIES

Animal Species	Route of Administration	LD50 mg/kg (95% Confidence Limits)	References
Rat, male	Oral	1,125 (*)	20,21
female	Oral	826 (747-914)	
Rat	Subcutaneous	>200	22
Mouse, male	Oral	1,041 (903-1,201)	20,21
female	Oral	1,363 (1,165-1,594)	
Mouse	Intraperitoneal	>250	23
Rabbit	Subcutaneous	>100, <200	22
	Intravenous	224 (179-282)	24
	Dermal	>200	24
Duck, mallard	Oral	1,490	25
Quail, bobwhite	Oral	1,000	25
Mink	Oral	503	25
Calf	Oral	Ca. 750	26, 27

* The data did not permit calculation of confidence limits.

The acute toxicity of DIMP was determined for a wide variety of aquatic organisms representing several trophic forms. These included primary producer organisms, primary consumers, and secondary consumers. They were exposed under a wide variety of water quality conditions to a range between 257 and 6,332 mg/L.[28] The bioconcentration factor for DIMP was experimentally examined in fish; essentially no bioconcentration was observed for bluegills continually exposed to ^{14}C-DIMP.[28]

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causes has not been established. Erythema multiforme has also been reported rarely.

Reports of purpura and allergic reactions such as wheal and flare at the injection site or urticaria have been extremely rare.

Forms of optic neuritis, including retrobulbar neuritis and papillitis may infrequently follow viral infections, and have been reported to occur 1 to 3 weeks following inoculation with some live virus vaccines.

Syncope, particularly at the time of mass vaccination, has been reported.

Very rarely encephalitis, febrile seizures, nerve deafness and other nervous system reactions have occurred in vaccinees. A cause-effect relationship has not been established.

DOSAGE AND ADMINISTRATION

FOR SUBCUTANEOUS ADMINISTRATION

Do not inject intravenously

The dosage of vaccine is the same for all persons. Inject the total volume (about 0.5 mL) of reconstituted vaccine subcutaneously, preferably into the outer aspect of upper arm. *Do not give immune serum globulin (ISG) concurrently with* MUMPSVAX.

During shipment, to insure that there is no loss of potency, the vaccine must be maintained at a temperature of 10°C (50°F) or less.

Before reconstitution, store MUMPSVAX at 2–8°C (36–46°F). *Protect from light.*

CAUTION: A sterile syringe free of preservatives, antiseptics, and detergents should be used for each injection and/or reconstitution of the vaccine because these substances may inactivate the live virus vaccine. A 25 gauge, ⅝" needle is recommended.

To reconstitute, use only the diluent supplied, since it is free of preservatives or other antiviral substances which might inactivate the vaccine.

Single Dose Vial—First withdraw the entire volume of diluent into the syringe to be used for reconstitution. Inject all the diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly. Withdraw the entire contents into a syringe and inject the total volume of restored vaccine subcutaneously.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

10 Dose Vial (available only to government agencies/institutions)—Withdraw the entire contents (7 mL) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 mL of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

50 Dose Vial (available only to government agencies/institutions)—Withdraw the entire contents (30 mL) of the diluent vial into the sterile syringe to be used for reconstitution and introduce into the 50 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. With full aseptic precautions, attach the vial to the sterilized multidose jet injector apparatus. Use 0.5 mL of the reconstituted vaccine for subcutaneous injection.

Each dose of MUMPSVAX contains not less than the equivalent of 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. MUMPSVAX, when reconstituted, is clear yellow.

HOW SUPPLIED

No. 4753—MUMPSVAX is supplied as a single-dose vial of lyophilized vaccine, **NDC 0006-4753-00**, and a vial of diluent.

No. 4584X, 4309—MUMPSVAX is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC 0006-4534-00**; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature (6505-01-037-6792, Ten Pack).

Available only to government agencies/institutions:

No. 4664X—MUMPSVAX is supplied as one 10 dose vial of lyophilized vaccine, **NDC 0006-4664-00**, and one 7 mL vial of diluent.

No. 4593X—MUMPSVAX is supplied as one 50 dose vial of lyophilized vaccine, **NDC 0006-4593-00**, and one 30 mL vial of diluent.

Storage

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2–8°C (36–46°F) and discard if not used within 8 hours.

A.H.F.S. Category: 80:12

DC 7680410 Issued March 1991

MUSTARGEN®, Trituration of (Mechlorethamine HCl for Injection, MSD), U.S.P. ℞

DESCRIPTION

MUSTARGEN® (Mechlorethamine HCl, MSD), an antineoplastic nitrogen mustard also known as HN2 hydrochloride, is a nitrogen analog of sulfur mustard. It is a white, crystalline, hygroscopic powder that is very soluble in water and also soluble in alcohol.

Mechlorethamine hydrochloride is designated chemically as 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride. The molecular weight is 192.52 and the melting point is 108–111°C. The empirical formula is $C_5H_{11}Cl_2N \cdot HCl$, and the structural formula is:

$$CH_3N(CH_2CH_2Cl)_2 \cdot HCl$$

Trituration of MUSTARGEN is a sterile, white crystalline powder for injection by the intravenous or intracavitary routes after dissolution. Each vial of MUSTARGEN contains 10 mg of mechlorethamine hydrochloride triturated with sodium chloride q.s. 100 mg. When dissolved with 10 mL Sterile Water for Injection or 0.9% Sodium Chloride Injection, the resulting solution has a pH of 3–5 at a concentration of 1 mg mechlorethamine HCl per mL.

CLINICAL PHARMACOLOGY

Mechlorethamine, a biologic alkylating agent, has a cytotoxic action which inhibits rapidly proliferating cells.

Pharmacokinetics and Metabolism

In water or body fluids, mechlorethamine undergoes rapid chemical transformation and combines with water or reactive compounds of cells, so that the drug is no longer present in active form a few minutes after administration.

INDICATIONS AND USAGE

Before using MUSTARGEN *see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED, Special Handling.*

MUSTARGEN, administered intravenously, is indicated for the palliative treatment of Hodgkin's disease (Stages III and IV), lymphosarcoma, chronic myelocytic or chronic lymphocytic leukemia, polycythemia vera, mycosis fungoides, and bronchogenic carcinoma.

MUSTARGEN, administered intrapleurally, intraperitoneally, or intrapericardially, is indicated for the palliative treatment of metastatic carcinoma resulting in effusion.

CONTRAINDICATIONS

The use of MUSTARGEN is contraindicated in the presence of known infectious diseases and in patients who have had previous anaphylactic reactions to MUSTARGEN.

WARNINGS

> Extravasation of the drug into subcutaneous tissues results in a painful inflammation. The area usually becomes indurated and sloughing may occur. If leakage of drug is obvious, prompt infiltration of the area with sterile isotonic sodium thiosulfate (⅙ molar) and application of an ice compress for 6 to 12 hours may minimize the local reaction. For a ⅙ molar solution of sodium thiosulfate, use 4.14 g of sodium thiosulfate per 100 mL of Sterile Water for Injection or 2.64 g of anhydrous sodium thiosulfate per 100 mL or dilute 4 mL of Sodium Thiosulfate Injection (10%) with 6 mL of Sterile Water for Injection.

Before using MUSTARGEN, *an accurate histologic diagnosis of the disease, a knowledge of its natural course, and an adequate clinical history are important. The hematologic status of the patient must first be determined. It ... stand the hazards and therapeutic effe... ful clinical judgment must be exercised ... the indication for its use is not clear ... used.*

As nitrogen mustard therapy may ... and rapid development of amyloidosis ... if foci of acute and chronic suppura... absent.

Usage in Pregnancy

Mechlorethamine hydrochloride can ... administered to a pregnant woman. ... shown to produce fetal malformations ... when given as single subcutaneous ... (2–3 times the maximum recommended ... are no adequate and well controlled ... women. If this drug is used during ... tient becomes pregnant while taking ... should be apprised of the potential ... Women of childbearing potential sh... becoming pregnant.

PRECAUTIONS

General

This drug is highly toxic and both ... be handled and administered wit... GEN is a powerful vesicant, it is ... travenous use, and in most insta... Inhalation of dust or vapors and ... membranes, especially those of t... Rubber gloves should be worn ... GEN. (See DOSAGE AND ADMI... SUPPLIED, *Special Handling*.)

Because of the toxicity of MUSTAR... side effects following its use, the... fort from the use of this drug ... neoplasms or in the terminal ... balanced against the limited ... will vary with the nature and the ... treatment. The routine use of ... widely disseminated neoplasm...

The use of MUSTARGEN ... thrombocytopenia, and anem... marrow by tumor carries a ... good response to treatment with ... from the bone marrow may be ... of bone marrow function. Ho... response or in patients who ... with chemotherapeutic agents ... ther compromised, and leuko... anemia may become more ... the patient.

Tumors of bone and nervous ti... therapy. Results are unpredicta... lignant tumors of different ty...

Precautions must be observed w... and x-ray therapy or other ... courses. Hematopoietic func... pressed by either form of the... GEN following x-ray therapy ... to the drug should be given un... recovered. In particular, irr... num, ribs, and vertebrae shor... mustard may lead to hematol...

MUSTARGEN has been rep... sive activity. Therefore, it sh... of the drug may predispose the ... fungal infection.

Hyperuricemia may develop ... GEN. The problem of urate ... pated, particularly in the tre... adequate methods for contro... instituted and careful atten... fluid intake before treatmen...

Since drug toxicity, especially ... failure, seems to be more co... kemia than in other conditio... this condition with great ca...

Extreme caution must be used ... mended dose. (See OVERDOS...

Laboratory Tests

Many abnormalities of re... function have been reported ... ease and receiving mechlore... renal, hepatic, and bone ma...

Carcinogenesis, Mutagenesis ...

Therapy with alkylating ag... be associated with an inc... nant tumor, especially whe... other antineoplastic agents ... Young-adult female RF mi... with four doses of 2.4 mg/k... tion) at 2-week intervals wit... An increased incidence of ...

...Painting mechlorethamine on ... to 33 weeks resulted in squa... ...ations in the Ames test, in *E.* ...chlorethamine caused chro... ...ity of plant and mammalian ... were produced in ICR/Ha ...
...tility in the rat at a daily dose ... for two weeks.

WARNINGS.

...rug is excreted in human milk. ...eted in human milk and be... ...us adverse reactions in nurs... ...N, a decision should be made ... or to discontinue the drug, ...rtance of the drug to the ...

...ildren have not been estab... ...Use of MUSTARGEN in ... MUSTARGEN has been ... III and IV, in combination ...OPP schedule). The MOPP ...udes mechlorethamine, vin... ...dnisone or prednisolone.

...*usually is accompanied by* ...

...bitis may result from direct ...ntima of the injected vein. ...prolonged contact with the ...ted pressure in the antebra... ...ior compression from se...

...s, including anaphy... ...vomiting and depression ... blood are dose-limiting ... the use of full doses of ... vertigo, tinnitus and ...quently. Rarely, hemo... ...eases as the lymphomas ... may be precipitated by ...cluding MUSTARGEN. ...malities have been re... ...mustard therapy. ... night in case sedation ... and vomiting usually ...drug. Emesis may disap... ...may persist for 24 hours. ...are as to precipitate vas... ...hemorrhagic tendency. ... addition to sedatives, ...nd vomiting. Anorexia, ...ccur.

...MUSTARGEN (total dose ... intravenous dose or di... ...of 0.2 or 0.1 mg/kg respec... ...mphocytopenia within 24 ...nificant granulocytopenia ... for 10 days to 3 weeks. ...atively infrequent and re... ...y is complete within two ...hrombocytopenia is vari... ...appearance and recovery ...nerally parallels the se... ...me cases severe thrombo... ...n the gums and gastroin... ...mall subcutaneous hemor... ... be transient and in most ...ormal platelet count. How... ...ollable depression of the ... may follow the usual dose ... patients with widespread ... previously treated with ...ay. Persistent pancytope... ...ances, hemorrhagic com... ...parinemia. Erythrocyte ... during the first 2 weeks ...ntly. Depression of the ...d up to 50 days or more ...

...aculopapular skin erup... ...ncratic and does not neces... ...se of the drug. Erythema ...Herpes zoster, a common ...nts with lymphomas, may ...ituted and on occasion may ...further treatment should be discontinued during the acute phase of this illness to avoid progression to generalized herpes zoster.

Reproductive: Since the gonads are susceptible to MUSTARGEN, treatment may be followed by delayed catamenia, oligomenorrhea, or temporary or permanent amenorrhea. Impaired spermatogenesis, azoospermia, and total germinal aplasia have been reported in male patients treated with alkylating agents, especially in combination with other drugs. In some instances spermatogenesis may return in patients in remission, but this may occur only several years after intensive chemotherapy has been discontinued. Patients should be warned of the potential risk to their reproductive capacity.

OVERDOSAGE

With total doses exceeding 0.4 mg/kg of body weight for a single course, severe leukopenia, anemia, thrombocytopenia and a hemorrhagic diathesis with subsequent delayed bleeding may develop. Death may follow. The only treatment in instances of excessive dosage appears to be repeated blood product transfusions, antibiotic treatment of complicating infections and general supportive measures.

The intravenous LD_{50} of MUSTARGEN is 2 mg/kg and 1.6 mg/kg in the mouse and rat, respectively.

DOSAGE AND ADMINISTRATION

Intravenous Administration

The dosage of MUSTARGEN varies with the clinical situation, the therapeutic response and the magnitude of hematologic depression. A total dose of 0.4 mg/kg of body weight for each course usually is given either as a single dose or in divided doses of 0.1 to 0.2 mg/kg per day. Dosage should be based on ideal dry body weight. The presence of edema or ascites must be considered so that dosage will be based on actual weight unaugmented by these conditions.

The margin of safety in therapy with MUSTARGEN *is narrow and considerable care must be exercised in the matter of dosage.* Repeated examinations of blood are *mandatory* as a guide to subsequent therapy. (See OVERDOSAGE.)

Within a few minutes after intravenous injection, MUSTARGEN undergoes chemical transformation, combines with reactive compounds, and is no longer present in its active form in the blood stream. Subsequent courses should not be given until the patient has recovered hematologically from the previous course; this is best determined by repeated studies of the peripheral blood elements awaiting their return to normal levels. It is often possible to give repeated courses of MUSTARGEN as early as three weeks after treatment.

Preparation of Solution for Intravenous Administration

This drug is highly toxic and both powder and solution must be handled and administered with care. Since MUSTARGEN is a powerful vesicant, it is intended primarily for intravenous use, and in most instances is given by this route. Inhalation of dust or vapors and contact with skin or mucous membranes, especially those of the eyes, must be avoided. Rubber gloves should be worn when handling MUSTARGEN. Should accidental eye contact occur, copious irrigation with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes, followed by 2 percent sodium thiosulfate solution. (See also box warning and *Special Handling.*)

Each vial of MUSTARGEN contains 10 mg of mechlorethamine hydrochloride triturated with sodium chloride q.s. 100 mg. In neutral or alkaline aqueous solution it undergoes rapid chemical transformation and is highly unstable. Although solutions prepared according to instructions are acidic and do not decompose as rapidly, they should be prepared immediately before each injection since they will decompose on standing. When reconstituted, MUSTARGEN is a clear colorless solution. *Do not use if the solution is discolored or if droplets of water are visible within the vial prior to reconstitution.*

Using a sterile 10 mL syringe, inject 10 mL of Sterile Water for Injection or 10 mL Sodium Chloride Injection into a vial of MUSTARGEN. With the needle (syringe attached) still in the rubber stopper, shake the vial several times to dissolve the drug completely. The resultant solution contains 1 mg of mechlorethamine hydrochloride per mL.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Special Handling

Due to the drug's toxic and mutagenic properties, appropriate precautions including the use of appropriate safety equipment are recommended for the preparation of MUSTARGEN for parenteral administration. The National Institutes of Health presently recommends that the preparation of injectable anti-neoplastic drugs should be performed in a Class II laminar flow biological safety cabinet and that personnel preparing drugs of this class should wear surgical gloves and a closed front surgical-type gown with knit cuffs. Several other guidelines for proper handling and disposal of anti-cancer drugs have been published and should be considered. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Accidental contact: Should accidental eye contact occur, copious irrigation with water, normal saline or a balanced salt ophthalmic irrigating solution should be instituted immediately, followed by prompt ophthalmologic consultation. Should accidental skin contact occur, the affected part must be irrigated immediately with copious amounts of water, for at least 15 minutes, followed by 2 percent sodium thiosulfate solution. (See also box warning.)

Technique for Intravenous Administration

Withdraw into the syringe the calculated volume of solution required for a single injection. *Dispose of any remaining solution after neutralization* (see below). Although the drug may be injected directly into any suitable vein, it is injected preferably into the rubber or plastic tubing of a flowing intravenous infusion set. This reduces the possibility of severe local reactions due to extravasation or high concentration of the drug. Injecting the drug into the tubing rather than adding it to the entire volume of the infusion fluid minimizes a chemical reaction between the drug and the solution. The rate of injection apparently is not critical provided it is completed within a few minutes.

Intracavitary Administration

Nitrogen mustard has been used by intracavitary administration with varying success in certain malignant conditions for the control of pleural, peritoneal, and pericardial effusions caused by malignant cells.

The technic and the dose used by any of these routes varies. Therefore, if MUSTARGEN is given by the intracavitary route, the published articles concerning such use should be consulted. *Because of the inherent risks involved, the physician should be experienced in the appropriate injection technics, and be thoroughly aware of the indications, dosages, hazards, and precautions as set forth in the published literature. When using* MUSTARGEN *by the intracavitary route, the general precautions concerning this agent should be borne in mind.*

As a general guide, reference is made especially to the technics of Weisberger et al. Intracavitary use is indicated in the presence of pleural, peritoneal, or pericardial effusion due to metastatic tumors. Local therapy with nitrogen mustard is used only when malignant cells are demonstrated in the effusion. Intracavitary injection is not recommended when the accumulated fluid is chylous in nature, since results are likely to be poor.

Paracentesis is first performed with most of the fluid being removed from the pleural or peritoneal cavity. The intracavitary use of MUSTARGEN may exert at least some of its effect through production of a chemical poudrage. Therefore, the removal of excess fluid allows the drug to more easily contact the peritoneal and pleural linings. For intrapleural or intrapericardial injection nitrogen mustard is introduced directly through the thoracentesis needle. For intraperitoneal injection it is given through a rubber catheter inserted into the trocar used for paracentesis or through a No. 18 gauge needle inserted at another site. This drug should be injected slowly, with frequent aspiration to ensure that a free flow of fluid is present. If fluid cannot be aspirated, pain and necrosis due to injection of solution outside the cavity may occur. Free flow of fluid also is necessary to prevent injection into a loculated pocket and to ensure adequate dissemination of nitrogen mustard.

The usual dose of nitrogen mustard for intracavitary injection is 0.4 mg/kg of body weight, though 0.2 mg/kg (or 10 to 20 mg) has been used by the intrapericardial route. The solution is prepared, as previously described for intravenous injection, by adding 10 mL of Sterile Water for Injection or 10 mL of Sodium Chloride Injection to the vial containing 10 mg of mechlorethamine hydrochloride. (Amounts of diluent of 50 to 100 mL of normal saline have also been used.) The position of the patient should be changed every 5 to 10 minutes for an hour after injection to obtain more uniform distribution of the drug throughout the serous cavity. The remaining fluid may be removed from the pleural or peritoneal cavity by paracentesis 24 to 36 hours later. The patient should be followed carefully by clinical and x-ray examination to detect reaccumulation of fluid.

Pain occurs rarely with intrapleural use; it is common with intraperitoneal injection and is often associated with nausea, vomiting, and diarrhea of 2 to 3 days duration. Transient cardiac irregularities may occur with intrapericardial injection. Death, possibly accelerated by nitrogen mustard, has

Continued on next page

Information on the Merck Sharp & Dohme products listed on these pages is the full prescribing information from product circulars in use October 1, 1991.

Background Document C, Reference 8

Edgewood Arsenal, 1974, *Chemical Agent Data Sheets,* Volume I, Special Report EO-SR-740001, Department of the Army, Edgewood Arsenal, Aberdeen Proving Ground, Md., Dec.

See Background Document B, Reference 15

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MANUAL OF MILITARY CHEMISTRY
VOLUME I - CHEMISTRY OF CHEMICAL WARFARE AGENTS

Siegfried Franke

1967

Processed for the

by the

U.S. DEPARTMENT OF COMMERCE/National Bureau of Standards/Institute for Applied Technology

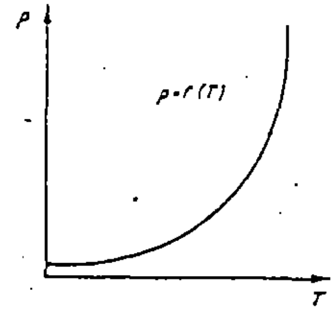


Figure 1.1. Vapor Pressure as a function of the temperature.

The temperature dependence of the vapor pressure can be approximately calculated by Regnault's formula

$$\lg p = A - \frac{B}{T}, \qquad (1.III)$$

where A and B are individual constants whose values can be calculated from two different boiling points T_1 and T_2 and their corresponding pressures p_1 and p_2, if the boiling points differ by at least 70°.

$$\text{a)}\quad \lg p_1 = A - \frac{B}{T_1}$$

$$\text{b)}\quad \lg p_2 = A - \frac{B}{T_2}$$

The chief numerical values required in the chemistry of chemical warfare agents are shown in Table 1.1.

Table 1.1. The constants A and B for calculating the vapor pressure according to Regnault.

Chemical Warfare Agent	A	B
Bis-(2-chloroethyl)-thioether	9.4819	3117.2
Cyanogen bromide	10.3282	2457.5
Diphenyl chloroarsine	7.8930	3288
Dipropoxy-(2)-phosphoryl fluoride	8.872	2671
Methyl dichloroarsine	8.6944	2281.7
Phosgene	7.5595	1326
Propoxy-(2)-methylphosphoryl fluoride	9.8990	2850.9
Trichloronitromethane	8.2424	2045.1

Thermodynamically the dependence of the vapor pressure on the temperature can be explained by the Clausius-Clapeyron equation (1.IV), in which the differential quotient dp/dT denotes the variation of the pressure with the temperature [1].

$$\frac{dp}{dT} = \frac{\Delta H_v}{T(V_g - V_{fl})} \qquad (1.IV)$$

ΔH_v = enthalpy of evaporation, or molar heat of evaporation.

In the case of a low vapor-pressure value the equation can be simplified by disregarding the molar volume V_{fl} of the liquid phase and assuming for V_g the validity of the general equation of state of ideal gases,

Table 3.2. Physical data for chloroacetophenone.

Boiling point	°C	139 ... 141 247 (245)
	mm Hg	14
Freezing point	°C	58 ... 59
p_s at 20°C	mm Hg	0.013
C_s at 20°C	mg/l	0.105
Vapor density		5.3
D_4^{20}	g/cm^3	1.321
Heat of vaporization	cal	89
Solubility:		
Water		0.1%
Organic solvents	Readily soluble in halogen alkanes, alkanoles, ether, carbon disulfide, benzene	
Chemical warfare agents	Trichloronitromethane, phosgene, sulfur mustard, cyanogen chloride	
Inorganic substances	Slightly soluble in $SnCl_4$, $TiCl_4$	

vapor pressure which develops suffices to make a terrain contaminated with chloroacetophenone impassable without protective masks. The lower threshold for detectable chloroacetophenone symptoms is $5 \cdot 10^{-4}$ mg/l.

Table 3.3. Vapor pressure and volatility of chloroacetophenone between -20°C and +50°C.

Temperature	°C	−20	−10	0	10	20	30	40	50
Vapor pressure	mm Hg	$1{,}7 \cdot 10^{-4}$	$5{,}6 \cdot 10^{-4}$	$1{,}7 \cdot 10^{-3}$	$4{,}5 \cdot 10^{-3}$	$1{,}3 \cdot 10^{-2}$	$3{,}1 \cdot 10^{-2}$	$7{,}2 \cdot 10^{-2}$	$1{,}6 \cdot 10^{-1}$
Volatility	mg/l	10^{-3}	$5 \cdot 10^{-3}$	$1{,}5 \cdot 10^{-2}$	$4{,}2 \cdot 10^{-2}$	$1{,}1 \cdot 10^{-1}$	$2{,}3 \cdot 10^{-1}$	$5{,}7 \cdot 10^{-1}$	1,2

The effect of chloroacetophenone vapors is dependent on the outside temperature. As Table 3.3 shows, the volatility below 10°C is too low for an effective concentration to develop. It is possible nevertheless to use it in cold seasons, in the form of an aerosol. Chloroacetophenone is sufficiently stable with respect to heat, and can therefore be used not only in shells and hand grenades, but also in low-temperature carbonation gases. It is principally used as an aerosol warfare agent.

The fact that chloroacetophenone does not decompose at its own boiling point makes it possible to pour the liquid product directly into shells and to mix it with low-carbonation mixtures and even with explosives, e.g. 2,4,6-trinitrotoluene, especially as these have approximately the same specific gravity.

Chloroacetophenone is practically indissoluble in water, but dissolves well in the usual organic solvents, such as chloralkanes, alkanoles, and benzene. It dissolves in certain proportions in some chemical warfare agents, such as sulfur mustard, phosgene, trichloronitromethane, and cyanogen chloride.

Depending on the density of poisoning and the local and meteorological conditions, chloroacetophenone solutions may be persistent for hours and days. A chloroacetophenone-chloropicrine solution mixed with trichloromethane is said to have a persistency in the woods of two hours in the summer and up to a week in the winter. In the open one hour in the summer and six hours in the winter is counted on.

3.1.2.3.3. *Chemical Properties*

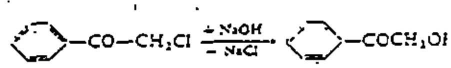
Chloroacetophenone is by structure a mixed aliphatic-aromatic ketone. As such it is relatively stable and slow to react. The well-known reactions of the aliphatic ketones with the carbonyl reagents such as hydroxyl amine and hydrazine occur here, too. On the other hand no hydrogen sulfite additive compound forms.

The thermal stability of chloroacetophenone is good; it is stable when detonated. It is only when exposed to a temperature above 300°C for a considerable period (15 minutes) that it is noticeably broken down, -- 1.5% at 300°C, 9% at 600°C, and about 30% at 750°C.

Hydrolysis. -- Even in water at boiling temperature chloroacetophenone is not hydrolyzed or not noticeably so.

Chloroacetophenone on the ground does not lose its properties even under a covering of snow, and after the snow melts it is again physiologically effective under correspondingly favorable weather temperatures; the same applies to chloroacetophenone poured into the ground.

The rate of hydrolysis is accelerated by alkalies, but is so slow at normal temperatures that this reaction is worthless for decontamination. A quantitative conversion is achieved only by boiling in alkali hydroxide solution, especially when alcoholic solutions are concerned. As a product of hydrolysis, oxymethyl phenyl ketone (oxyacetophenone) is formed, -- crystals which melt at 86°C.


(3.13)

Further Reactions of the Chlorine Atom. -- The chlorine atom of chloroacetophenone can also be substituted by other reactions. With alkali iodides in alcohol-water solutions iodoacetophenone forms, an acicular crystalline substance.

$$C_6H_5COCH_2Cl \xrightarrow[Cl^-]{+I^-} C_6H_5COCH_2I \qquad (3.14)$$

As in the case of the aliphatic halogenated ketones, chloroacetophenone exhibits conversion with sodium sulfide in alcoholic or alcohol-water solutions as the best-suited reaction for a possible contamination.

$$2C_6H_5COCH_2Cl \xrightarrow[-2NaCl]{+Na_2S} (C_6H_5COCH_2)_2S \qquad (3.15)$$

The bis-(acetylphenyl)-thioether* (freezing point 74°C) shows no physiological effect.

By boiling with sodium thiosulfate the sodium salt of acetylphenyl thiosulfonic acid is obtained.

$$C_6H_5COCH_2 \cdot S_2O_3Na$$

Condensation Reactions. -- As a ketone, chloroacetophenone reacts among other things with hydroxyl amine.

At room temperature in aqueous methanol solution it forms with hydroxyl aminohydrochloride the compound ω-chloroacetophenone oxime (chloromethylphenyl ketoxime; 3.16), a colorless crystalline compound (freezing point 88.5° to 89°C), which has a powerful lachrymogenic effect and, like the halogenated oximes (cf. section 5.4), produces long-lasting skin irritations (rashes). This compound has not been seriously mentioned in the literature before as a possible chemical warfare agent.

*Phenacyl thioether.

possible chemical warfare agent at the present time.

A bromochlorine compound is 2-chloroethyl-2'-bromoethyl thioether, $Cl\cdot CH_2CH_2\cdot S\cdot CH_2CH_2\cdot Br$, Bp_{12} 125° to 132°C, melting point 24°C. The analogous iodine compound, bis-(2-iodoethyl)-thioether, is a yellow crystalline compound (melting point 62° to 70°C) whose properties correspond to those of the compounds already discussed.

5.1.4.3. 2.2'-Bis-(2-chloroethylthio)-Diethyl Ether

$$O\begin{cases} CH_2CH_2\cdot S\cdot CH_2CH_2Cl \\ CH_2CH_2\cdot S\cdot CH_2CH_2Cl \end{cases}$$

Oxygen mustard

Bp_2 174°C; $Bp_{0.001}$ 120°C

Melting point −30 ... −38°C

D_4^{20} 1,2311

2.2'-bis-(2-chloroethylthio)-diethyl ether, like the compounds discussed below, was produced and investigated in England during the Second World War [37]. This compound has a considerably greater skin-damaging effect than bis-(2-chloroethyl)-thioether. In general its physiological effectiveness is reported to be about 3.5 times as great as that of sulfur mustard.

The reaction of concentrated hydrogen chloride with bis-(2-hydroxyethyl)-thioether at 110°C produces a mixture of 60% bis-(2-chloroethyl)-thioether and 40% 2.2'-bis-(2-chloroethylthio)-diethyl ether (the so-called HT mixture). The oxygen mustard cannot be removed from the mixture by distillation.

Preparation in the pure form can be accomplished by chlorination of 2.2'-bis-(2-hydroxyethylthio)-diethyl ether with thionyl chloride in a chloroform solution below 40°C.

$$O\begin{cases} CH_2CH_2\cdot S\cdot CH_2CH_2OH \\ CH_2CH_2\cdot S\cdot CH_2CH_2OH \end{cases} \xrightarrow[-SO_2,\ -H_2O]{+SOCl_2} O\begin{cases} CH_2CH_2\cdot S\cdot CH_2CH_2Cl \\ CH_2CH_2\cdot S\cdot CH_2CH_2Cl \end{cases} \qquad (5.43)$$

The hydroxy compound is obtained from bis-(2-chloroethyl)-ether and 2 mole 2-hydroxyethane thiol in an alcoholic solution of sodium in accordance with (5.44). It is a compound that melts at 32°C and has a high boiling point ($Bp_{2.5}$ 215°C).

$$O\begin{cases} CH_2CH_2Cl \\ CH_2CH_2Cl \end{cases} \xrightarrow[-2HCl]{+2NaSCH_2CH_2OH} O\begin{cases} CH_2CH_2\cdot S\cdot CH_2CH_2OH \\ CH_2CH_2\cdot S\cdot CH_2CH_2OH \end{cases} \qquad (5.44)$$

Oxygen mustard is a colorless liquid which dissolves readily in the usual organic solvents such as benzene and acetone. It is less soluble in alcohol. It is insoluble in water.

Chemically it behaves like bis-(2-chloroethyl)-thioether. Usually the same products occur in chemical reactions, as e.g. N-(p-toluenesulfonyl)-bis-(2-chloroethyl)-sulfimine in the reaction with chloramine.

The analogous iodine and bromine compounds are more unstable, especially 2.2'-bis-(2-iodoethylthio)-diethyl ether. Its use in tactical mixtures has been considered.

ethine with turbulence. Either by refrigeration or by controlling the course of the reaction and regulating the supply of gas, the reaction temperature is kept below 50°C.

The oily liquid mixture produced is treated with semi-concentrated hydrochloric acid or with ethanolamine hydrochloride depending on the catalyst used. The purification process ends with the distillative separation of the 2-chloroethenyl dichloroarsine under reduced pressure.

By the new method an 85 to 90% yield of an almost pure, almost odorless product is obtained. The proportion of the secondary product in the industrial product is about 10%. Tertiary arsine, mixed with arsine(III)chloride, is contained in the industrial product only in minute amounts.

Preparation in the Laboratory. -- The substance is prepared from arsenic(III)chloride and ethine, with aluminum(III)chloride serving as a catalyst.

45 g $AsCl_3$ and 15 g anhydrous $AlCl_3$ are put into the reaction vessel (a 250-ml flask), which is provided with a stirrer, a gas-inlet tube, and a gas-outlet tube. 6 to 8 l of ethine is conducted through the reaction mixture with stirring and cooling; the ethine is previously purified with sulfuric acid and dried with calcium chloride. The reaction temperature should not exceed 35°C. The reaction product is slowly poured into about 200 ml of hydrochloric acid at a temperature below 0°C and then stirred 10 to 15 minutes. Washing again with hydrochloric acid is recommended. The oily stratum formed is distilled under a reduced pressure of 20 to 22 mm Hg. The first fraction, up to 60°C, contains arsenic(III)chloride; the 2-chloroethenyl dichloroarsine passes over at 80 to 100°C as the second fraction, while the secondary byproduct will pass over at 120 to 140°C and the tertiary above 140°C as the third fraction.

5.3.3.2. *Physical Properties*

In the older literature the satements concerning the physical properties of 2-chloroethenyl dichloroarsine are contradictory, since for a long time no one was in a position to produce a pure product. For military purposes a stabilized industrial product was tolerated.

The industrial product has a strong, penetrating geranium odor. The purified product is odorless. Industrial lewisite is an oily, darkbrown liquid with a congealing point at about -10° to -15°C. Below 10°C the industrial lewisite becomes noticeably more viscous.

By reason of the unsaturated structure of these compounds the prerequisites for stereoisomeric phenomena are present. The trans and cis forms of 2-chloroethenyl dichloroarsine have been isolated and their physical constants determined [55].

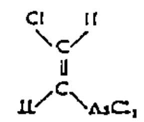
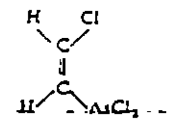
The cis isomer is formed in thermal decomposition and by irradiating the trans isomer with ultraviolet light (300 to 400 nm).

The volatility of trans lewisite at 20°C is given as 4.5 mg/l, while the volatility of ordinary lewisite containing both components amounts to about 2.3 mg/l.

Above 190°C, the boiling point of ordinary lewisite, decomposition phenomena appear.

The solubility of lewisite in water is slight, about 0.5 g/l. It is readily soluble in organic solvents such as halogen alkanes, alkanols, and gasoline. It is also readily soluble in vegetable and animal fats and in oils.

Because of its good miscibility with other chemical warfare agents lewisite is suitable for use in the preparation of tactical mixtures.

		Trans-2-Chloroethenyl Dichloroarsine (Trans-Lewisite) (ordinary lewisite)	Cis-2-Chloroethenyl Dichloroarsine (Cis-Lewisite) (iso-lewisite)
			
Bp_{750}	°C	196.6	169.8
Fp†	°C	-2.4	-44.7
p_s at 25°C	mm Hg	0.40	1.562
D_4^{25}	g/cm^3	1.3793	1.8598
D_4^t	g/cm^3	1.9210-0.00167 · t	1.9018-0.00168 · t
n_D^{25}		1.6076	1.5898

†Congealing point.

Thus e.g. it mixes with sulfur mustard, diphosgene, and various chemical warfare agents which are organic compounds of phosphorus.

The power to penetrate materials such as leather, rubber, wood, and textiles is more marked in lewisite than in the mustards.

5.3.3.3. *Chemical Properties*

Thermal dissociation of 2-chloroethenyl dichloroarsine yields the secondary and tertiary arsines, which under some circumstances decompose further into molecular cleavage products. Even with very brief heating, such as occurs for instance in explosions, the decomposition phenomena are considerable, so that when pure, odorless lewisite is used odoriferous components are produced, especially in the form of tertiary lewisite.

Lewisite is relatively unstable, a fact that is to be attributed to its $-AsCl_2$ structure and its unsaturated character.

When the product is stored for a long time in metal containers the development of acid cleavage products must be avoided. Lewisite is catalytically converted by iron into the secondary and the tertiary product. High-quality steels are not affected. Aluminum and aluminum alloys are greatly corroded by lewisite.

Storage of lewisite in shells and bombs is made possible by stabilizers and corrosion inhibitors.

There are no significant differences between the two lewisite isomers in chemical properties. They can be distinguished by their differing behavior in cold alkali lyes. The trans form is more unstable than the cis form.

Hydrolysis. — The $-AsCl_2$ group as an acid chloride determines the hydrolysis of lewisite. It is relatively rapidly hydrolyzed, giving off hydrochloric acid and forming 2-chloroethenyl arsinic oxide.

$$ClCH{=}CH{-}AsCl_2 \xrightarrow[-2HCl]{+HOH} ClCH{=}CH{-}As{=}O \qquad (5.78)$$

The rapid hydrolysis is among the most important shortcomings of this chemical warfare agent. The opinion formerly held that lewisite could be used for poisoning water because of the poisonous 2-chloroethenyl arsinic oxide that is formed can no longer be defended. For such purposes more effective compounds are available today.

Its tendency to hydrolysis permits the use of lewisite only under the most favorable meteorological conditions.

2-chloroethenyl arsinic oxide is a white crystalline substance that melts at 143°C. The oxide of the cis isomer melts at 131°C. It acts as a blood poison and in suitable solvents also shows a considerable skin-irritant effect.

Weak alkalies suffice to promote hydrolysis. Dilute ammonia solutions are adequate to convert 2-chloroethenyl dichloroarsine into the oxide. The effect of alkalies even without heat leads to complete decomposition of the molecule.

$$ClCH{=}CH{-}AsCl_2 \xrightarrow{+6NaOH} Na_3AsO_3 + 3NaCl + CH{\equiv}CH + 3H_2O \qquad (5.79)$$

Trans lewisite dissolves in cold sodium hydroxide solution without the development of ethine and with only the formation of the sodium salt of arsinic acid.

This behavior serves to distinguish the two isomers. At temperatures above 40°C cis lewisite is also completely decomposed by alkali lyes. The conversion of lewisite with alkali lyes is quantitative. It is a decontamination reaction and can also be used for analysis.

The lewisite molecule is decomposed by aqueous sodium sulfide solutions with the formation of arsenic sulfide and ethine.

$$2ClCH{=}CHAsCl_2 \xrightarrow[-6NaCl]{+3Na_2S} As_2S_3 + 2CH{\equiv}CH \qquad (5.80)$$

Other reactions of the $-AsCl_2$ *group.* -- Hydrogen sulfide in alcoholic solution with 2-chloroethenyl dichloroarsine forms an arsinic sulfide with a powerful irritant effect.

$$Cl{-}CH{=}CH{-}AsCl_2 \xrightarrow[-2HCl]{+H_2S} ClCH{=}CH{-}As{=}S \qquad (5.81)$$

The most important reaction for decontamination is oxidation. By such oxidizing agents as hydrogen peroxide, nitric acid, and chloride of lime, the arsine is converted into the arsonic acid.

$$ClCH{=}CH{-}AsCl_2 \xrightarrow[-2HCl]{+O+2HOH} ClCH{=}CH{-}As(=O)(OH)_2 \qquad (5.82)$$

2-chloroethenyl arsonic acid consists of acicular crystals melting at 130 to 131°C. It can be prepared relatively easily by the action of chlorine on an aqueous lewisite solution. The solution is concentrated and the crystals obtained from water. The cis isomeric compound has a lower melting point (90 to 91°C). The arsonic acid produces no physiological effects.

Chlorination. -- The chlorination of 2-chloroethenyl dichloroarsine is dependent on the medium. If the compound is dissolved in organic solvents, especially halogen alkanes, and treated with chlorine or bromine, an addition of the halogen atoms to the double bond of the ethenyl group takes place.

Chlorination in aqueous solutions leads to the formation of the very unstable tetrachloroarsine, which is converted by the action of the water into the arsonic acid. Under suitable conditions the cleavage of tetrachloroarsine into arsenic(III)chloride and dichloroethene is possible, whereupon the arsenic(III)chloride undergoes further hydrolysis.

Background Document C, Reference 10

Goldman, M. and J.C. Dacre, 1989, "Lewisite: Its Chemistry, Toxicology, and Biological Effects," *Rev. Environ. Contam. Toxicol.* 110:76-115.

This document can be obtained through most local or university libraries.

ITTIIANE, CPMS, CPMSC

Drinking Water Health Advisory:

MUNITIONS I

United States Environmental Protection Agency
Office of Drinking Water Health Advisories

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[202] 659-8090
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Library of Congress Catalog Card Number

94-69091

Drinking water health advisory. Munitions / edited by
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p. cm.
Includes bibliographical references.

1. Organic water pollutants--Toxicology. 2. Munitions--Toxicology 3. Drinking water--Health aspects--United States.
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PRINTED IN THE UNITED STATES OF AMERICA
1 2 3 4 5 6 7 8 9 0

Printed on acid-free paper

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1,4-DITHIANE

Mary B. Deardorff, Ph.D., B. Ram Das, Ph.D., and Welford C. Roberts, Ph.D.

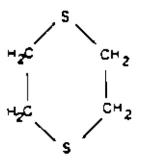
I. General Information and Properties

1,4-Dithiane (diethylene disulfide) is a crystalline, organo-sulfur compound associated with the storage of mustard gas (Berkowitz *et al.*, 1978). At room temperature it may exist as white monoclinic crystals. The X-ray analyses indicate that 1,4-dithiane has a centro-symmetrical chair configuration consistent with the absence of a dipole moment. 1,4-Dithiane is a volatile crystal, and its odor has been described as very unpleasant to almost odorless, suggesting that different impurities may influence its odor. It is moderately soluble in water, sublimes at modest temperatures without being destroyed, readily steam distills, and volatilizes with alcohol well below its own boiling point. General chemical and physical properties of 1,4-dithiane are presented in Table 1.

1,4-Dithiane concentration in mustard gas (bis (2-chloroethyl) sulfide) increases over time (Berkowitz, 1982). Although the source of 1,4-dithiane in mustard gas has not been documented under controlled laboratory conditions, mustard degradation is considered the most likely source of the compound (Rohrbaugh *et al.*, 1988a,b; Stein *et al.*, 1946). Degradation of a mustard simulant, 2-chloroethyl ethyl sulfide (CEES), has been shown to yield 1,4-dithiane, presumably via the degradation of dimeric sulfonium ion intermediates as shown in Figure 1 (Rohrbaugh *et al.*, 1988a; D'Agostino and Provost, 1985). Trace quantities of water were thought to have initiated the degradation process. The primary degradation product of CEES after one or two years of storage at ambient temperatures was determined to be 1,4-dithiane (Rohrbaugh *et al.*, 1988a,b). Rohrbaugh *et al.* (1988a,b) also suggested that information on the degradation rate of mustard could be useful in determining the age of mustard gas and its impurities.

1,4-Dithiane has been found in groundwater at the Rocky Mountain Arsenal (RMA), Colorado, and preliminary sampling results detected 1,4-dithiane in groundwater at the Aberdeen Proving Ground, Maryland. Its presence in groundwater has been associated with mustard gas deposits, production, or demilitarization operations at these facilities (Berkowitz *et al.*, 1978; U.S. ATSDR, 1989). The highest concentration of 1,4-dithiane in groundwater (9,678 μg/L) has been observed at the RMA, where it is classified as a Priority 2 chemical (Berkowitz *et al.*, 1978). At the Aberdeen Proving Ground, preliminary groundwater sampling results detected a 1,4-dithiane concentration of 1 mg/L (1,000 μg/L) (U.S. ATSDR, 1989). The major environmental transport route expected for 1,4-dithiane is through surface and groundwater due to its solubility in water and relatively low octanol/water partition coefficient (<100) (Berkowitz, 1982).

Table 1. General Chemical and Physical Properties of 1,4-Dithiane

Property	Value	
CAS No	505-29-3	
Synonyms[a]	Diethylene disulfide, Diethylene sulfide, *p*-Dithiane, 1,4-Dithiacyclohexane, Tetrahydro-1,4-Dithiin, Triethylene trisulfide (early 1920s misnomer), Tetramethylene 1,4-disulfide (German equivalent)	
Molecular weight	120.13[a], 120.23[b], 120.24[c]	
Empirical formula[a]	$C_4H_8S_2$	
Structure[a]		
Physical state	White, monoclinic crystals at 25°C[a], moderately clear, prism shaped crystals[d]	
Melting point	111°-112°C[d] (ranging from 108°-113°C)[a]	
Boiling point	199°-200°C (1 atm, 769 mm Hg)[a,d]	
Heat of combustion	-793.2 kcal/mole at 298° K (estimated)[a]	
Heat of formation	1.8 kcal/mole at 298° K (estimated)[a]	
Vapor pressure	0.8 mm Hg at 25°C (estimated)[a,e], 51.4 mm Hg at 111°C over liquid (estimated)[a]	
Octanol-water partition coefficient (K_{ow})	44 (estimated)[a], log K_{ow} = 0.77[e]	
Stability characteristics	Stable in sesame oil stored at -20°C for 90 days[f]	
Solubility characteristics	1 Water	11.88 g/L (0.099 mole/L) at 25°C (estimated)[a], 2.9 mg/mL[c]
	2 Methanol	21 mg/mL at 25°C[f] (approximate)
	3 Acetone	79 mg/mL at 25°C[f] "
	4 Hexane	17 mg/mL at 25°C[f] "
	7 Sesame oil	40 mg/mL at 25°C[f] "
	5 DMSO	98 mg/mL at 35°C[f] "
	6 Tween 80	99 mg/mL at 35°C[f] "
	(Soluble in ethanol, ether, chloroform, benzene, and carbon disulfide)[a]	

SOURCE: Adapted from [a]Berkowitz *et al.* (1978), [b]U.S. EPA (1989), [c]Aldrich Chemical Co. (1988), [d]Weast (1988), [e]Small (1983), [f]Thompson *et al.* (1989)

1,4-Dithiane is produced in the United States for research purposes only (Schieferstein, 1987). Berkowitz *et al.* (1978) reports that there are numerous procedures for synthesizing 1,4-dithiane. A convenient method that yields respectable quantities (≥ 50% by weight) involves the reaction of an ethylene halide (chloride or bromide) with sulfide (sodium or potassium) in ethanol with subsequent heating in phenol to increase the yield. From simple hydroxysulphides, such as $S(C_2H_4{\cdot}OH)_2$, $C_2H_4(S{\cdot}C_2H_4{\cdot}OH)_2$, and $S(C_2H_4{\cdot}S{\cdot}C_2H_4{\cdot}OH)_2$, Bell *et al.* (1927) synthesized dithiane by boiling each compound for 2 hours with hydrogen bromide saturated phenol.

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II. Occurre

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exist in the United States. G
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results indicate that 1,4-dith
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groundwater at the Aberdeen
health concern because of the
(U.S. ATSDR, 1989).

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chlorination in water treatment

Although no published
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operties of 1,4-Dithiane

p-Dithiane, 1,4-Dithiacyclohexane,
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quivalent)

derately clear, prism shaped crystals[d]

mm Hg at 111°C, over liquid (estimated)[e]

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mL[e]
mL at 25°C[f] (approximate)
mL at 25°C[f]
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each compound for 2 hours

1,4-Dithiane did not inhibit phytogrowth in *Brassica rapa* L. and *Medicago sativa* L. and it did not demonstrate antibacterial activity to gram-negative and gram-positive bacteria (Inamori *et al.*, 1990).

II. Occurrence and Sources of Exposure

The potential for human exposure to 1,4-dithiane in drinking water may exist in the United States. Groundwater contamination has been detected at the Rocky Mountain Arsenal (RMA), Colorado, (Berkowitz, 1982). Preliminary results indicate that 1,4-dithiane is in on-site groundwater at the Aberdeen Proving Ground, Maryland (U.S. ATSDR, 1989). In addition, Small (1983) has suggested that the potential exists for 1,4-dithiane contamination at Fort McClellan, Alabama, where mustard gas was used or spilled before 1973. Chemical decontaminants were applied to contaminated areas at Fort McClellan, but the potential for persistent soil contamination has not been assessed (Small, 1983).

The highest known concentrations of 1,4-dithiane in the groundwater of the United States were recorded at the RMA where they range from 3,600 to 9,678 μg/L (Berkowitz, 1982). There is a potential for human exposures through groundwater. 1,4-Dithiane is expected to be transported through surface and groundwater and might well migrate off-site (Berkowitz, 1982). Although preliminary results indicate that only 1 mg/L (1,000 μg/L) 1,4-dithiane is in groundwater at the Aberdeen Proving Ground, the site is considered a public health concern because of the population centers living on and around the site (U.S. ATSDR, 1989).

Other potential pathways of environmental contamination, in addition to groundwater, are surface water, on-site soils, and volatilization of the contaminant in ambient air (U.S. ATSDR, 1989). The vapor pressure of 1,4-dithiane is sufficiently high to allow some vapor transport from soil and water to air (Berkowitz *et al.*, 1978). Human exposure could occur through inhalation of volatilized contaminants or contaminants entrained in air during remedial operations at contaminated sites (U.S. ATSDR, 1989). 1,4-Dithiane can be readily chlorinated by chlorine at room temperature in carbon tetrachloride (Berkowitz *et al.*, 1978), but no information was found regarding the rate of chlorination in aqueous media or possible implications for rate or extent of chlorination in water treatment systems.

Although no published data were found, there is a potential for the occurrence of occupational exposure to compounds related to 1,4-dithiane in places such as pesticide manufacturing facilities and research laboratories. The antitumor activity of novel pyrimidine nucleoside analogues of 1,4-dithiane were investigated and shown to be somewhat effective *in vitro* (Hronowski and Szarek, 1982).

D. Excretion

No data on the excretion of 1,4-dithiane from the body were found.

V. Health Effects

A. Humans

No studies on the health effects of 1,4-dithiane in humans were found.

B. Animals

1. Short-term Exposure

a. Acute

Oral LD_{50} values for 1,4-dithiane administered by gavage to Fischer 344 rats were 3,680 mg/kg for males and 2,768 mg/kg for females (Mayhew and Muni, 1986). A single dose of 1,4-Dithiane suspended in corn oil was administered to five rats/sex/dose in doses of 2,818; 3,162; and 3,981 mg/kg. In addition, five females were administered 1,778 mg/kg and five males received 3,548 mg/kg 1,4-dithiane in corn oil. No information was found regarding vehicle control animals. Fasted body weights on the day of dosing ranged for males from 207 to 245 grams and for females from 153 to 177 grams. Animals were observed at least once daily for both mortality and clinical signs of toxicity. Animals found dead were subjected to necropsy as soon as possible after death. All surviving animals were sacrificed on day 14 and necropsied. The necropsy involved examinations of all external surfaces and orifices as well as abdominal, thoracic, and pelvic cavities and their viscera.

All mortalities occurred at 1 to 6 days post-dosing. Mortality was greater in females than in males at doses above 1,778 mg/kg (Table 2). Male deaths were observed at or above 3,548 mg/kg and female deaths at or above 2,818 mg/kg dose levels. The higher mortality in females than in males was not explained. Deaths were observed within 72 hours in four of five males that received the highest dose (3,981 mg/kg) and within 24 hours in two males that received 3,548 mg/kg 1,4-dithiane. Among females administered the highest dose, the same ratio as males (4/5) died within the same 72 hour period. Of the two females that died in the 3,162 mg/kg dose group, one died within 24 hours, and the other died on the 6th day after dosing. At the 2,818 mg/kg dose, four of five females died; three within 24 hours and one within 72 hours. No deaths were reported at the lowest dose (1,778 mg/kg).

Table 2. Two Week
Oral G

Dose Level (mg/kg)	Number of Animals
1,778	5 Females
2,818	5/Sex
3,162	5/Sex
3,548	5 Males
3,981	5/Sex

[a]To keep the 1,4-dithiane dosing solution constan
[b]LD_{50}s are 3,680 mg/kg for males, 2,768 mg/kg

SOURCE Adapted from Mayhew and Muni (19

A variety of antemortem c
in both males and females at all
(Table 3). The most frequent
central nervous system and gas
dose level exhibited a d, w
sometime during the first 48 ho
at every dose also showed lacri
or stained fur in the perianal re
before day 6 and not thereafte
reported to have had yellow/br
to 9.

At necropsy of animals f
gastrointestinal abnormalities,
(Table 4). These abnormalities
white discolorations of the org
left ovary was discovered in on
finding reported in the animals

b. Primary Irritation, De

No primary irritation or d
found.

Ophthalmologic examinati
dithiane toxicity in gavaged rats
Groups of rats (30 rats/sex/dos
daily by oral gavage for 90 day

Table 2. Two Week Mortality of Fischer 344 Rats Dosed by Oral Gavage with 1,4-Dithiane[a,b]

Dose Level (mg/kg)	Number of Animals	Number of Compound-Related Deaths		Mortality (%)	
		Males	Females	Males	Females
1,778	5 Females	—	0	—	0
2,818	5/Sex	0	4	0	80
3,162	5/Sex	0	2	0	40
3,548	5 Males	2	—	40	—
3,981	5/Sex	4	4	80	80

[a]To keep the 1,4-dithiane dosing solution constant at 17 mg/kg body weight, all animals received split dosing within 2 to 3 hours
[b]LD_{50}s are 3,680 mg/kg for males, 2,768 mg/kg for females, and 3,473 mg/kg for the combined sexes

SOURCE Adapted from Mayhew and Muni (1986)

A variety of antemortem clinical signs of 1,4-dithiane toxicity were reported in both males and females at all dose levels during the 14-day observation period (Table 3). The most frequently observed clinical signs were associated with central nervous system and gastrointestinal tract functions. All animals at every dose level exhibited ataxia, which was observed in 95% of the animals at sometime during the first 48 hours after dosing and not thereafter. Some animals at every dose also showed lacrimation, crusty eyes and noses, lethargy, and damp or stained fur in the perianal region. All clinical signs of toxicity were exhibited before day 6 and not thereafter with one exception. A high-dose female was reported to have had yellow/brown stained fur in the perianal region on days 4 to 9.

At necropsy of animals found dead prior to terminal sacrifice, lung and gastrointestinal abnormalities, including liver changes, were typically reported (Table 4). These abnormalities were characterized by red, black/dark, pale, or white discolorations of the organs or their contents. A solitary, red cyst of the left ovary was discovered in one high-dose female. This was the only abnormal finding reported in the animals that survived to terminal sacrifice.

b. Primary Irritation, Dermal Sensitization, and Ophthalmologic Effects

No primary irritation or dermal sensitization studies of 1,4-dithiane were found.

Ophthalmologic examinations were conducted during a 90-day study of 1,4-dithiane toxicity in gavaged rats (Schieferstein, 1987; Schieferstein *et al.*, 1988). Groups of rats (30 rats/sex/dose) were administered 1,4-dithiane in sesame oil daily by oral gavage for 90 days at 0, 105, 210, and 420 mg/kg/day. Ophthalmo logic examinations were performed on all animals before dosing began and during week 12 of dosing. The nature of the ophthalmologic examination was not specified. No treatment-related ophthalmologic effects were associated with 1,4-dithiane after 12 weeks of dosing.

Table 3. Incidence of Antemortem Clinical Signs in Fischer 344 Rats Dosed by Oral Gavage with 1,4-Dithiane

Clinical Findings	Dose Level (mg/kg) 1,778	2,818		3,162		3,548	3,981	
	5/F[a]	5/M	5/F	5/M	5/F	5/M	5/M	5/F
Ataxia (days 0-6)[b]	5	5	5	5	5	5	5	5
Lacrimation (days 0-2)	3	4	5	4	4	5	4	5
Crusty eye (days 2-6)	5	3	1	5	4	3	1	1
Crusty nose (days 1-4)	1	3	2	3	2	1	1	1
Lethargy (days 0-6)	1	0	2	3	3	4	2	5
Damp perianal fur (days 0-5)	2	1	0	0	0	1	0	4
Yellow/brown stained perianal fur (days 2-9)	1	0	2	0	2	0	0	1
Prostration (days 1-2)	0	1	2	1	2	0	3	0
Muscle tremors (days 2-6)	0	0	1	0	2	0	0	0
Red stained fur around eyes (days 1-2)	0	0	0	2	2	0	0	0
Squinting (day 2)	0	0	1	0	0	0	0	0
Crusty muzzle (days 0-6)	0	0	0	2	1	0	0	0
Few stools (days 2-3)	0	0	0	0	2	3	0	0
No stools (days 1-2)	0	0	0	0	2	1	0	0
Irregular breathing (day 2)	0	0	0	0	0	0	1	0
Hyperactivity (day 0)	0	0	0	0	1	0	0	0
Emaciation (days 4-6)	0	0	0	0	1	0	0	0

[a]Number of animals over sex of animals in each treatment group
[b]Range of days that clinical signs were observed for all groups

SOURCE Adapted from Mayhew and Muni (1986)

Mayhew and Muni (198
while studying the acute tox
in corn oil and administere
rats/sex/dose received 2,818;
five females were adminis
received 3,548 mg/kg 1,4-di
reported. The animals wer
mortality and signs of toxici
dose levels during the first
Lacrimation was reported in
the study and not thereafter (

c. *Subacute*

In a 14-day range finding
maximum tolerated dose, Sc
sesame oil by gavage daily to
210, or 420 mg/kg/day. Dos
(age range: 31-40 days). The
effects and mortality. Body
measured weekly. M lity,
water or food consump wer
weight gain were measured in
dose of 420 mg/kg/day. Afte
dithiane was found to be conta
animal carcinogen. No gro
hematologic evaluations were

2. *Longer-term Exposure*

a. *13-Week Studies*

Only one 90-day study o
(1987) conducted a subchronic
female CD rats. At the start o
40 days. Groups of rats (30 r
1,4-dithiane suspended in ses
were weighed on the first day
and doses were adjusted accor
the target concentration. Rou
per day.

Mayhew and Muni (1986) observed some antemortem ocular effects in rats while studying the acute toxicity of 1,4-dithiane. The compound was suspended in corn oil and administered by oral gavage to Fischer 344 rats. Five rats/sex/dose received 2,818; 3,162 or 3,981 mg/kg 1,4-dithiane. In addition, five females were administered 1,778 mg/kg 1,4-dithiane, and five males received 3,548 mg/kg 1,4-dithiane. No information on control animals was reported. The animals were observed at least once daily for 14 days for mortality and signs of toxicity. Antemortem crusty eyes were reported at all dose levels during the first 6 days of the study but not thereafter (Table 3). Lacrimation was reported in both sexes at all doses during the first 48 hours of the study and not thereafter (Table 3).

c. *Subacute*

In a 14-day range finding study, which was conducted to select a 90-day maximum tolerated dose, Schieferstein (1987) administered 1,4-dithiane in sesame oil by gavage daily to groups of six CD rats/sex/dose at 0, 25, 50, 100, 210, or 420 mg/kg/day. Dosing began when the rats were five weeks of age (age range: 31-40 days). The animals were observed daily for subacute toxic effects and mortality. Body weight and food and water consumption were measured weekly. Mortality, overt toxicity, and treatment-related effects on water or food consumption were not observed. Nonsignificant decreases in body weight gain were measured in males (5.3%) and females (8.0%) at the highest dose of 420 mg/kg/day. After the 14-day study had been completed, the 1,4-dithiane was found to be contaminated with 0.2% methylene chloride, a known animal carcinogen. No gross pathologic, histologic, clinical chemistry, or hematologic evaluations were performed.

2. *Longer-term Exposure*

a. *13-Week Studies*

Only one 90-day study of 1,4-dithiane toxicity was found. Schieferstein (1987) conducted a subchronic oral toxicity study of 1,4-dithiane in male and female CD rats. At the start of the study, the animals ranged in age from 31 to 40 days. Groups of rats (30 rats/sex/dose) were gavaged daily for 90 days with 1,4-dithiane suspended in sesame oil at 0, 105, 210, or 420 mg/kg/day. Rats were weighed on the first day of the dosing period and each succeeding week, and doses were adjusted accordingly. All dosing solutions were within ±5% of the target concentration. Routine observations of the animals were made twice per day.

Table 4. Incidence of Abnormalities Following Oral Gavage with 1,4-Dithiane at Necropsy of Rats Found Dead Prior to Sacrifice[a,b]

Organ Abnormality	Dose Level (mg/kg) 2,818	3,162	3,548	3,981	
	4/F	2/F	2/M	4/M	4/F
Dark or white colored stomach contents	1	0	2	4	2
Diffuse red or dark red discolorations of lungs	1	1	0	2	4
Multiple black or red discolorations of glandular stomach	1	1	0	4	1
Red, dark, or white fluid/material in intestinal tract	1	1	1	2	2
Yellow fluid discoloration around mouth	0	0	1	3	2
Diffuse red discolorations of intestines	2	1	0	0	2
Pale or tan discolorations of liver	3	0	0	0	1
Black discolored fur around rectum	0	1	0	0	0
Saliva around mouth	0	0	0	1	0

[a]Oral gavage of rats (5/sex/dose) with 1,4-dithiane in corn oil at 1,178 (females), 2,818, 3,162, 3,548 (males), and 3,981 mg/kg
[b]No mortality observed at 1,178 mg/kg dose, one high-dose female that survived to terminal sacrifice (14 days) had a solitary red cyst on the left ovary, other surviving animals at all doses had no reported abnormalities

SOURCE Adapted from Mayhew and Muni (1986)

All surviving animals were terminally sacrificed at 90 days and subjected to a complete necropsy. All high-dose and control animals received detailed histopathology. When an animal was removed from the study before terminal sacrifice (*e.g.*, due to death or moribund condition), only its nose was examined histologically. Liver, thymus, spleen, and brain were weighed at terminal sacrifice. An ophthalmologic examination was conducted before the start of dosing and during week 12 of dosing. The activities of serum aspartate aminotransferase, alanine aminotransferase, serum sorbitol dehydrogenase, amylase, and lactic acid dehydrogenase isoenzymes as well as a complete blood count with leukocyte differential and reticulocyte count were performed on six animals per sex in the treatment and control groups on the day before dosing began and on days 30, 60, and 90 of the study period. Seven animals died before the 90-day sacrifice and were excluded from statistical analyses. Their deaths were not considered to be treatment related. The cause of death in six of the seven animals was attributed to gavage accident. The cause of death of the seventh animal (a male dosed at 420 mg/kg/day for 7 days) was not reported. Anisotropic crystals were found in the nasal olfactory mucosa of the seventh animal.

No overt toxicity, treatment-related mortality, or ophthalmologic changes were reported in any of the animals. No significant treatment-related changes occurred in body weight and in food and water consumption. There was, however, a significant ($p < 0.05$) treatment-related increase in female liver, male

kidney, and male thymus
The female liver to body
significantly higher (p <0.
with control organ weight
spleen was significantly gr
greater but only in animals
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Morphologic lesions
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lesions were found in all
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nasal septum) of both sex
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observed in 2 of 30 'es
at both the 210 mg/kg/day
observed in 24 of 29 fema
(30/30) at both the 210 mg
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Lesions were most severe
some instances, crystals ha
cavity. Crystals were not
Crystals that were closely a
cases, focal osseous and car
were observed in the kidne
chronic active inflammation

Liver lesions were ob
Hypertrophy of the centrilo
of distortion of lobular arch
Cytoplasmic vacuolation o
was seen in 7 of the 30 hig

kidney, and male thymus weights as well as a decrease in female brain weight. The female liver to body weight ratio of high-dose (420 mg/kg/day) rats was significantly higher ($p < 0.05$) than the control ratio. When compared ($p < 0.05$) with control organ weights, female brain weight was significantly less, female spleen was significantly greater, and male kidney and spleen were significantly greater but only in animals receiving the lowest dose (105 mg/kg/day). Based on these data and evidence of anatomical changes in only female liver and male kidney (described in subsequent paragraphs), the author (Schieferstein, 1987) considered the effects on female liver and kidney weights to be the most important of the organ weight changes.

Morphologic lesions in the nose, liver (females only), and kidney (males only) were observed in animals administered 420 mg 1,4-dithiane/kg/day. Nasal lesions were found in all treatment groups (Table 5). The most prominent pathological finding was bilateral deposition of anisotropic crystals of an undetermined chemical composition in the nasal olfactory mucosa (turbinates and nasal septum) of both sexes at all doses, but severity was greatest in the intermediate- and high-dose groups. Schieferstein (1987) presumed that the crystals were not comprised of the test chemical because 1,4-dithiane, which is readily soluble in alcohol, would have dissolved in the increasing concentrations of ethanol used to prepare slides for histopathologic examination. Crystals were observed in 2 of 30 males at the 105 mg/kg/day dose and in all males (28/28) at both the 210 mg/kg/day and 420 mg/kg/day dose levels. Crystals were observed in 24 of 29 females at the 105 mg/kg/day dose and in all females (30/30) at both the 210 mg/kg/day and 420 mg/kg/day dose levels. No crystals were evident in control animals. The severity of the lesions was measured by the number of crystals, which varied widely in size and shape, and degree of inflammation. It was assumed that the presence of the crystals in the mucosa caused a granulomatous inflammatory reaction, characterized by phagocytosis. Lesions were most severe in the posterior portion of the nasal cavity, and in some instances, crystals had penetrated the olfactory epithelium into the nasal cavity. Crystals were not observed in nasal respiratory epithelial mucosa. Crystals that were closely associated with bone and cartilage, induced in some cases, focal osseous and cartilaginous inflammation and degeneration. Crystals were observed in the kidneys in one animal that also had chronic cystitis and chronic active inflammation of the kidneys.

Liver lesions were observed only in high-dose (420 mg/kg/day) females. Hypertrophy of the centrilobular hepatocytes, which caused a minimal amount of distortion of lobular architecture, was found in 26 of 30 females in this group. Cytoplasmic vacuolation of hepatocytes in the periportal region of the lobules was seen in 7 of the 30 high-dose females.

Table 5. Incidence of Lesions in CD Rats Dosed by Oral Gavage for 90 Days with 1,4-Dithiane[a]

		Dose Level (mg/kg/day)			
Lesion	Sex	0	105	210	420
Nasal crystals	M	0/28[b]	2/30	28/28	28/28
	F	0/30	24/29	30/30	30/30
Hypertrophy of centrilobular hepatocytes	F	0/30	0/29	0/30	26/30
Cytoplasmic vacuolization of hepatocytes	F	0/30	0/29	0/30	7/30
Eosinophilic cytoplasmic renal granules	M	0/28	0/30	0/28	26/28

[a]Lesions in animals surviving to terminal sacrifice
[b]Number of animals with lesion over number of animals in dose group at terminal sacrifice

SOURCE Adapted from Schieferstein (1987), Schieferstein *et al.* (1988)

A morphologic kidney change was observed in high-dose (420 mg/kg/day) males. Cytoplasmic alteration, characterized by multiple eosinophilic granules or droplets of varying size in the cytoplasm of the renal convoluted tubules, was observed in 26 of 28 males in the high-dose group. The distal convoluted tubules appeared to be the most severely affected.

Although some treatment-related hematological and clinical chemistry changes appeared to have significant ($p < 0.05$) dose-response relationships, the differences between dosed and control values were not significant. A significant treatment-related decrease ($p < 0.05$; linear trend analysis) was measured in the female reticulocyte count, but there was no difference for this hematologic indicator between dosed and control animals. Significant ($p < 0.05$; linear trend analysis) treatment-related decreases were found in female amylase and sorbitol dehydrogenase, in male lactate dehydrogenase isoenzyme 3, and in lactate dehydrogenase isoenzymes 1 and 5 of both sexes. However, there were no significant differences between the dosed and control animals for these enzymes at any dose (except amylase in low-dose rats on day 30) or at any collection period. Schieferstein (1987) submitted that a variety of logistical factors, such as removal to different quarters before sacrifice, as well as the possible effect of aging on the animals might account for the treatment-related decreases. The gavage study of Schieferstein (1987) suggests a LOAEL of 105 mg/kg/day, the lowest dose tested for 1,4-dithiane in rats.

b. Lifetime Studies

No chronic or lifetime toxicity studies using 1,4-dithiane were found.

3. ***Reproductive Effects***

No studies on the repr

4. ***Developmental Toxicit***

No studies on the deve

5. ***Carcinogenicity***

No studies on the carci

6. ***Genotoxicity***

The mutagenic potent *Salmonella*/Mammalian M nonmutagenic (Sano and K dithiane were found.

Using the Ames assa TA1535, TA1537, and TA1 range of concentrati 5, 1 and absence of exogenous S dose levels represent a con toxic level (the maximum mammalian metabolic acti induced rat liver, was ap simulating *in vivo* metaboli toxicity test was used t concentrations of 1,4-dithia confirmed using four know (1985) determined from the mutagenic with and withou

VI. Quanti

No studies on the hea

Based on an acute Mayhew and Muni (1986) and 2,768 mg/kg for female dose of 1,4-dithiane in co Mortality was greater in fe above 3,548 mg/kg and frequently reported clinical at all doses), lacrimation, cr

3. *Reproductive Effects*

No studies on the reproductive effects of 1,4-dithiane were found.

4. *Developmental Toxicity*

No studies on the developmental effects of 1,4-dithiane were found.

5. *Carcinogenicity*

No studies on the carcinogenicity of 1,4-dithiane were found.

6. *Genotoxicity*

The mutagenic potential of 1,4-dithiane was evaluated using the Ames *Salmonella*/Mammalian Microsome Mutagenicity Assay; 1,4-dithiane was nonmutagenic (Sano and Korte, 1985). No other mutagenicity studies with 1,4-dithiane were found.

Using the Ames assay, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to 1,4-dithiane over a 1,000-fold range of concentrations (5, 1, 0.2, 0.04, 0.008, 0.0016 mg/plate) in the presence and absence of exogenous S9 metabolic activation (Sano and Korte, 1985). The dose levels represent a concentration range that decreases from the minimum toxic level (the maximum or limit dose) by a dilution factor of five. The mammalian metabolic activator (S9), which was derived from Aroclor 1254 induced rat liver, was applied to increase the sensitivity of the assay by simulating *in vivo* metabolic activation of the test compound. A range-finding toxicity test was used to determine the maximum limit and sublethal concentrations of 1,4-dithiane. The responsiveness of the tester strains was confirmed using four known mutagens as positive controls. Sano and Korte (1985) determined from these tests that in the Ames assay, 1,4-dithiane was not mutagenic with and without metabolic activation.

VI. Quantification of Toxicological Effects

No studies on the health effects of 1,4-dithiane in humans were reported.

Based on an acute toxicity study of 1,4-dithiane in Fischer 344 rats, Mayhew and Muni (1986) reported oral LD_{50} values of 3,680 mg/kg for males and 2,768 mg/kg for females. Rats (5 rats/sex/dose) were gavaged with a single dose of 1,4-dithiane in corn oil at doses ranging from 1,778 to 3,981 mg/kg. Mortality was greater in females than in males. Deaths occurred in males at or above 3,548 mg/kg and in females at or above 2,818 mg/kg. The most frequently reported clinical signs of 1,4-dithiane toxicity were ataxia (all animals at all doses), lacrimation, crusty eye, lethargy, and crusty nose in both males and females. Necropsy of animals that died before terminal sacrifice (day 14) revealed gastrointestinal, lung, and liver (females only) abnormalities characterized by discolorations of these organs and their contents. A solitary ovarian cyst was reported in one high-dose female that survived to terminal sacrifice. No other abnormalities were reported on necropsy in any other animals that survived to terminal sacrifice.

In a subacute, 14-day range-finding gavage study of CD rats administered 1,4-dithiane in sesame oil (0, 25, 50, 100, 210, or 420 mg/kg/day), Schieferstein (1987) found no mortality, overt toxicity, or treatment-related effects on water or food consumption. The purpose of the study was to identify a maximum tolerated dose for a 90-day toxicological study. A nonsignificant ($p < 0.05$) decrease in body weight gain in both sexes was evidenced at the highest dose (420 mg/kg/day). No gross pathologic, histologic, clinical chemistry, hematologic, or ophthalmologic examinations were performed.

A subchronic, 90-day oral gavage study of CD rats that were administered 0, 105, 210, or 420 mg/kg/day (30/sex/dose) showed morphologic lesions in the nose, liver (females only), and kidney (males only) as well as significant ($p < 0.05$) changes in some organ weights (Schieferstein, 1987; Schieferstein *et al.*, 1988). No overt toxicity, enzyme and hematologic effects, treatment-related mortality, and ophthalmologic changes were found. The occurrence of anisotropic crystals, with associated tissue necrosis and inflammation, in the nasal olfactory mucosa of both sexes at all doses was the most prominent finding. Liver and kidney lesions occurred only at the highest dose. Female spleen weight was greater, female brain was less, and male kidney and spleen weights were greater than control organ weights at the 105 mg/kg/day dose. In addition, significant treatment-related increases in the weight of female liver and male kidney and thymus as well as a decrease in female brain weight were observed. However, based on morphological evaluations, the increased liver and kidney weights were regarded as the most important of the organ weight changes.

In the Ames *Salmonella*/Mammalian Microsome Mutagenicity Assay, Sano and Korte (1985) determined that 1,4-dithiane was not mutagenic in the presence and absence of metabolic activation.

A. One-day Health Advisory

Short-term studies of 1,4-dithiane were judged to be unsuitable for deriving a One-day Health Advisory (HA) value. Neither the LD_{50} study in Fischer 344 rats (Mayhew and Muni, 1986) nor the subacute study of 1,4-dithiane toxicity in CD rats (Schieferstein, 1987) established dose-response relationships for 1,4-dithiane toxicity. These studies were carried out primarily to establish LD_{50} values and as a range-finding study to determine the maximum tolerated dose for a 90-day subchronic study. It was not possible to establish a NOAEL or LOAEL for either of these studies. The Longer-term HA value for a 10 kg child, 0.4 mg/L (400 μg/L), is used as a conservative estimate for the One-day HA value.

B. Ten-day Health Advisory

The available data were considered to be unsuitable for determining the Ten-day HA value for 1,4-dithiane. The Schieferstein (1987) 14-day range finding study did not establish a dose-response relationship for determining a NOAEL or LOAEL. No mortality or overt toxicity, and no significant treatment-related effects on body weight and water and food consumption were observed in CD rats (six rats/sex/dose) administered 1,4-dithiane in sesame oil by oral gavage daily at 0, 25, 50, 100, 210, and 420 mg/kg/day dose levels. The rats were not examined for potential gross, pathologic, histologic, clinical chemistry, hematologic, or ophthalmologic effects. The Longer-term HA value for a 10 kg child, 0.4 mg/L (400 μg/L), is used as a conservative estimate for the Ten-day HA value.

C. Longer-term Health Advisory

The LOAEL of 105 mg/kg/day is used in the derivation of the Longer-term HA. It is based on the 90-day gavage rat study (Schieferstein, 1987), which is the only study of appropriate length that was found. Morphologic lesions in the nose, liver (females only), and kidney (males only) as well as occasional changes in the weights of female liver and brain, and male kidney and thymus were observed. Nasal lesions were observed in both sexes of all treatment groups (105, 210, and 420 mg/kg/day). Even at the lowest dose, 83% (24/29) of the females and 7% (2/30) of the males developed nasal lesions. Also at the 105 mg/kg/day dose, female spleen weight was greater, female brain was less, and male kidney and spleen weights were greater than organ weights in control animals ($p < 0.05$). However, based on the morphological evaluations, the authors regarded the increased liver and kidney weights to be the more important effects. A significant ($p < 0.05$) decrease from control values in female amylase was shown at the 105 mg/kg/day dose, 30-day collection period. However, Schieferstein (1987) considered the biological significance of this finding unclear because the amylase assay could not distinguish between salivary and pancreatic amylase, and no abnormalities were evidenced from pathologic examination in either the pancreas or salivary glands. Liver and kidney lesions were reported only at the highest dose.

The Longer-term HA for a 10 kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(105\ \text{mg/kg/day})\ (10\ \text{kg})}{(1{,}000)\ (3)\ (1\ \text{L/day})} = 0.35\ \text{mg/L}\ \ (\text{rounded to } 0.4\ \text{mg/L})$$

where:

105 mg/kg/day	=	LOAEL, based on morphologic evidence in rats of nasal lesions at this and higher doses (Schieferstein 1987; Schieferstein *et al.*, 1988)
10 kg	=	assumed weight of a child.
1 L/day	=	assumed water consumption of a 10 kg child
1,000	=	uncertainty factor (UF), chosen in accordance with NAS/EPA guidelines. This UF includes a factor of 10 for intraspecies variability, a factor of 10 for interspecies variability, and a factor of 10 for use of a LOAEL in the absence of a NOAEL.
3	=	additional uncertainty factor based on the high incidence of nasal olfactory lesions in female rats (24/29), database deficiencies (*e.g.*, lack of reproductive and developmental toxicity studies, and studies with other species), and a consideration for exposure duration.

The Longer-term HA for a 70 kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(105\ \text{mg/kg/day})\ (70\ \text{kg})}{(1{,}000)\ (3)\ (2\ \text{L/day})} = 1.225\ \text{mg/L}\ \ (\text{rounded to } 1.0\ \text{mg/L})$$

where:

105 mg/kg/day	=	LOAEL, based on morphologic evidence in rats of nasal lesions at this and higher doses (Schieferstein, 1987; Schieferstein *et al*, 1988).
70 kg	=	assumed weight of an adult.
2 L/day	=	assumed water consumption of a 70 kg adult.
1,000	=	uncertainty factor (UF), chosen in accordance with NAS/EPA guidelines. This UF includes a factor of 10 for intraspecies variability, a factor of 10 for interspecies variability, and a factor of 10 for use of a LOAEL in the absence of a NOAEL
3	=	additional uncertainty factor based on the high incidence of nasal olfactory lesions in female rats (24/29), database deficiencies (*e g*, lack of reproductive and developmental toxicity studies, and studies with other species), and a consideration for exposure duration

D. Lifetime Health Advisory

No acceptable long-term (chronic or lifetime) toxicity studies for 1,4-Dithiane were found. Therefore, the 90-day gavage rat study discussed above (Schieferstein, 1987) will be used to derive the Reference Dose (Rfd) for 1,4-Dithiane.

Morphological lesions in the nose, liver (females only) and kidneys (males only), as well as occasional changes in the weights of female liver and brain, and male kidney and thymus were observed. Nasal lesions were observed in both sexes of all the treatment groups (105, 210, and 420 mg/kg/day). Even at the lowest dose, 83% (24/29) of the females and 7% (2/30) of the males developed nasal lesions. Also at the 105 mg/kg/day dose, female spleen weight was greater, female brain weight was less, and male kidney and spleen weights were greater than the organ weights of control animals ($p<0.05$). Liver and kidney lesions were reported at the highest dose. Based on the morphological evaluations, the authors regard the increase liver and kidney weights to be the more important effects. A LOAEL of 105 mg/kg/day was reported based on morphological evidence in rats of nasal lesions at this and higher doses (Schieferstein, 1987; Schieferstein et al., 1988).

The Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(105\ \text{mg/kg/day})}{(1{,}000)(10)} = 0.0105\ \text{mg/kg/day}\quad \text{(rounded to 0.01 mg/kg/day)}$$

where:

105 mg/kg/day	=	LOAEL, based on morphologic evidence in rats of nasal lesions at this and higher doses (Schieferstein, 1987, Schieferstein *et al.*, 1988).
1,000	=	uncertainty factor (UF), chosen in accordance with NAS/EPA guidelines. This UF includes a factor of 10 for intraspecies variability, a factor of 10 for interspecies variability, and a factor of 10 for use of a LOAEL in the absence of a NOAEL.
10	=	An additional Modifying Factor of 10 is applied to account for the high incidence of nasal olfactory lesions in female rats (24/29), database deficiencies (*e g*, lack of reproductive and developmental toxicity studies, and studies with other species), and a consideration for exposure duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$\text{DWEL} = \frac{(0.01\ \text{mg/kg/day})\ (70\ \text{kg})}{(2\ \text{L/day})} = 0.350\ \text{mg/L}\quad \text{(rounded to 0.4 mg/L)}$$

where

0.01 mg/kg/day	=	RfD.
70 kg	=	assumed weight of an adult.
2 L/day	=	assumed water consumption of a 70-kg adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = (0.4\ \text{mg/kg/day})\ (0.2) = 0.08\ \text{mg/L}$$

where:

0.4 mg/L	=	DWEL.
0.2	=	assumed relative source contribution (20%) from drinking water.

E. Quantification of Carcinogenic Potential

No studies on the potential carcinogenicity of 1,4-dithiane were found. Therefore, no estimation of excess cancer risk has been made. 1,4-Dithiane was not mutagenic in *Salmonella* assays with and without metabolic activation. Based on the EPA classification scheme (U.S. EPA, 1986), 1,4-Dithiane is classified in U.S. EPA Group D; not classifiable as to human carcinogenicity.

Even though 1,4-dithiane is not classifiable as to human carcinogenicity, it should be noted that it is found in the presence of mustard gas, which is carcinogenic (U.S. EPA, 1991). Inhalation of sulfur mustard has been associated with lung cancers that developed in war veterans and factory workers who were exposed to the agent during battlefield operations or factory production activities, respectively. Sulfur mustard administered subcutaneously, intravenously, or by inhalation exposure also produced lung adenomas in mice. It is a DNA alkylating agent and therefore a strong genotoxic and mutagenic agent in mammalian and nonmammalian test systems.

VII. Other Criteria, Guidance, and Standards

The American Conference of Governmental Industrial Hygienists and the Occupational Safety and Health Administration have not determined a Threshold-Limit-Value, Short-Term-Exposure-Limit or Permissible-Exposure-Limit for 1,4-dithiane. A thorough literature search produced no information on existing standards, criteria, or guidance on 1,4-dithiane.

VI

Gas chromatography (
applied methods found in
magnetic resonance (NMR)
structure of 1,4-dithiane.

D'Agostino and Prov
ionization detection (GC-F
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extracted by ultrasonic vib
grade chloroform. The chi
analyses were conducted or
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D'Agostino *et al.* (198
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1,4-dithiane prior to toxico
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concentration of 1 mg/mL
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conditions are presented in

DATA DEFICIENCIES, PROBLEM AREAS, AND RECOMMENDATIONS FOR ADDITIONAL DATABASE DEVELOPMENT FOR *p*-CHLOROPHENYL METHYL SULFIDE, -SULFOXIDE, AND -SULFONE (PCPMS, PCPMSO, AND $PCPMSO_2$)

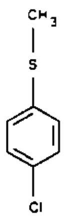
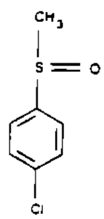
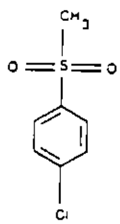
Margaret E. Brower, Ph.D., Mary B. Deardorff, Ph.D., and Welford C. Roberts, Ph.D.

I. General Information

p-Chlorophenyl methyl sulfide (PCPMS), *p*-chlorophenyl methyl sulfoxide (PCPMSO), and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$) are three distinct chemical species with differences in appearance, boiling point, and other physical properties. *p*-Chlorophenyl methyl sulfide appears as a colorless liquid at room temperature, PCPMSO as a waxlike solid, and $PCPMSO_2$ as a white crystalline solid (Fairfield Chemical Co., 1985a-c). All three are combustible compounds, decomposing upon combustion to release toxic and hazardous vapors. The general physical and chemical properties of PCPMS (CAS No. 123-09-1), PCPMSO (CAS No. 934-73-6), and $PCPMSO_2$ (CAS No. 98-57-1), are presented in Table 1.

All three compounds are intermediates in the manufacture of the herbicide Planavin®, but they are also produced by other means. *p*-Chlorophenyl methyl sulfide is synthesized via two processes: (1) methylation of the *p*-chlorobenzenethiol with either chloromethane or dimethyl sulfate in the presence of alkali; and (2) pyrolysis of S-*p*-chlorophenyl-O-methyl dithiocarbonate. *p*-Chlorophenyl methyl sulfoxide is found in trace amounts in $PCPMSO_2$. It arises from incomplete oxidation of the sulfide with hydrogen peroxide. It can be manufactured by a variety of methods; however, industrial production utilizes a mixture of oxygen and nitrogen dioxide in the oxidation process. The PCPMSO analog can be produced in the environment via oxidation of PCPMS in air following discharge of the sulfide (Miller *et al.*, 1976). The $PCPMSO_2$ analog can be synthesized via vigorous oxidation of either PCPMS or PCPMSO; however, oxidation of PCPMS is 50 times faster than oxidation of PCPMSO. The $PCPMSO_2$ also can be made from chloroaniline via substitution of the amino group with sulfur dioxide followed by methylation. Friedel-Crafts acylation of chlorobenzene with methanesulfonyl chloride followed by recrystallization can also be used. Only a few domestic companies produce these three chemicals (Table 2).

Table 1. Chemical and Physical Properties of *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)

Property	Sulfide	Sulfoxide	Sulfone	Reference
CAS No	123-09-1	934-73-6	98-57-7	Miller *et al* (1976)
Synonyms	*p*-Chloro-thioanisole,4-chlorothioanisole, methyl-*p*-chlorophenyl sulfide, methyl-4-chloro-phenyl sulfide	4-Chlorophenyl sulfoxide, methyl-4-chlorophenyl sulfoxide, methyl-4-chlorophenyl sulfoxide	4-Chlorophenyl methyl sulfone, methyl-4-chlorophenyl sulfone	Sax (1984)
Empirical formula	C_7H_7ClS	C_7H_7ClSO	$C_7H_7ClSO_2$	Sax (1984)
Structure				Miller *et al* (1976)
Molecular weight	158 65	174 65	190 65	Miller *et al* (1976)
Melting point	17-19°C	37-48°C	92-99°C	Miller *et al* (1976), Fairfield Chemical (1985a-c)
Boiling point (at 760 mm)	220-224°C	—	—	—
Density	1 202 g/mL (at 49°C)	—	—	Miller *et al* (1976)
Solubility water, mg/L	Insoluble	Insoluble	Insoluble	Fairfield Chemical (1985a-c)
Conversion factors (in air)				
ppm (v/v) to mg/m^3 (20°C)	1 ppm = 6 5 mg/m^3	1 ppm = 7 1 mg/m^3	1 ppm = 7 8 mg/m^3	
mg/m^3 to ppm (v/v)	1 mg/m^3 = 0 15 ppm	1 mg/m^3 = 0 14 ppm	1 mg/m^3 = 0 13 ppm	

II. Occurrence and Sources of Exposure

Information concerning occupational and environmental exposure is limited. Occupational exposure to *p*-chlorophenyl methyl sulfide (PCPMS), *p*-chlorophenyl methyl sulfoxide (PCPMSO), and *p*-chlorophenyl methyl sulfone ($PCPMSO_2$) may occur during manufacturing and munitions incorporation. The wastewaters could contaminate groundwater, soil used for agriculture, and public drinking water supplies. However, quantitative data are not available.

blood levels for all three analogs peaked at about 24 hours. Excretion was primarily in the urine with constant amounts excreted daily for 7 days. Elimination from the blood appeared to follow zero-order kinetics indicating saturability for all three analogs. Although PCPMSO cleared more slowly from the blood than PCPMS or $PCPMS_2$, there were no significant differences reported for the blood levels of the different analogs. Recovery of radioactivity in 7 days was somewhat less with the sulfide (26%) than with the sulfoxide (50%) or sulfone (42%). Elimination in feces was less than 5% of the total dose administered for all analogs.

V. Health Effects

A. Humans

No studies on the health effects of *p*-chlorophenyl methyl sulfide (PCPMS), -sulfoxide (PCPMSO), and -sulfone ($PCPMSO_2$) in humans were found.

B. Animals

1. Short-term Exposure

a. Acute

1) PCPMS

In an acute, oral toxicity study, Thake *et al.* (1979) gavaged Fischer 344 rats with a single dose of PCPMS dissolved in corn oil and observed the animals twice daily for mortality and toxic symptoms. Ten rats/sex/dose, except two female dose groups, each with 20 rats, were treated with the compound. Ten rats/sex served as controls. The dose levels, which ranged from 398 to 708 mg/kg in males and 355 to 794 mg/kg in females, had been established to cover a range of 0-100% mortality. At all treatment levels in both sexes, there was an immediate decrease in locomotor activity. At the higher doses, this was followed by a loss of coordination, prostration, loss of consciousness, severe lacrimation, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within 4 hours in some rats at the highest dose. No toxicity or mortality was observed in controls. Table 3 presents the LD_{50}s for PCPMS, which were higher for males (619 mg/kg) than for females (479 mg/kg).

In a similar, acute gavage study with $B_6C_3F_1$ mice (10/sex/dose, except one male treatment group with 20 mice), Thake *et al.* (1979) administered PCPMS dissolved in corn oil and observed the mice twice daily for mortality and toxic symptoms. The dose levels, established to induce 0-100% mortality, ranged from 501 to 1,122 mg/kg in males and 631 to 1,000 mg/kg in females. Ten mice/sex served as controls. At all treatment levels in both sexes, there was an immediate decrease in locomotor activity. At the higher doses, this was followed by a loss of coordination, prostration, loss of consciousness, severe lacrimation, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within hours in some mice at the highest dose. No toxicity or mortality was observed in controls. The LD_{50}s for PCPMS were higher for males (877 mg/kg) than for males (672 mg/kg) (Table 3).

Table 3. Acute Oral LD_{50} Values for *p*-Chlorophenyl Methyl Sulfide, -Sulfoxide, -Sulfone (PCPMS, PCPMSO, and $PCPMSO_2$)

Chemical	Species/Strain	LD_{50} (mg/kg) Male	LD_{50} (mg/kg) Female	Effects
PCPMS	Mouse/$B_6C_3F_1$	877	672	Toxic signs included an immediate decrease in locomotor activity, prostration, loss of consciousness, labored respiration, and death. Severe lacrimation was characteristic of animals treated with sulfide and sulfoxide analogs
	Rat/F344	619	479	
PCPMSO	Mouse/$B_6C_3F_1$	328	440	
	Rat/F344	611	463	
$PCPMSO_2$	Mouse/$B_6C_3F_1$	600	606	
	Rat/F344	529	400	

SOURCE Adapted from Thake *et al.* (1979)

In an acute dermal toxicity study, Thake *et al.* (1979) applied gauze sponges with PCPMS in acetone to the shaved backs of Fischer 344 rats (2/sex/dose) for 24 hours and observed the animals daily for 14 days. The dose levels were 0, 1,000, 2,190, or 5,630 mg/kg. All animals at the highest dose died within 24 hours following removal of the gauze. Also, at the highest dose, locomotor activity immediately decreased, followed by a loss of coordination, prostration, severe lacrimation, diarrhea, loss of consciousness, labored respiration, and death. Similar, but less severe, toxic symptoms occurred in the 2,190 mg/kg treatment group and were noted for 7 days. Rats in the 1,000 mg/kg group showed decreased locomotion for approximately 24 hours following removal of the gauze.

2) PCPMSO

In an acute, oral toxicity study, Thake *et al.* (1979) gavaged Fischer 344 rats (10/sex/dose, except two male dose groups with 20 rats) with PCPMSO dissolved in corn oil and observed the animals twice daily for mortality and toxic symptoms. The dose levels, which ranged from 398 to 794 mg/kg in males and 316 to 631 mg/kg in females, had been established to produce 0-100% mortality. Ten rats/sex served as controls. The results were the same as those for PCPMS.

The LD_{50}s for PCPMSO were higher for males (611 mg/kg) than for females (463 mg/kg) (Table 3).

In a similar, acute gavage study with $B_6C_3F_1$ mice (10/sex/dose, except one female treatment group with 20 mice), Thake *et al.* (1979) gave PCPMSO dissolved in corn oil and observed the mice twice daily for mortality and toxic symptoms. The dose levels, which had been established to produce 0-100% mortality, ranged from 158 to 501 mg/kg in males and 251 to 631 mg/kg in females. Ten mice/sex served as controls. The results were essentially the same as those for PCPMS. The LD_{50}s for PCPMSO were higher for females (440 mg/kg) than for males (328 mg/kg) (Table 3).

In an acute dermal toxicity study, Thake *et al.* (1979) applied gauze sponges with PCPMSO in acetone to the shaved backs of Fischer 344 rats (2/sex/dose) for 24 hours and observed the animals daily for 14 days. The dose levels were 0, 1,000, 2,190, or 5,630 mg/kg. No deaths occurred with this analog. However, at the highest dose, locomotor activity immediately decreased, followed by a loss of coordination, prostration, severe lacrimation, diarrhea, loss of consciousness, and labored respiration. A gradual recovery followed. Similar, but less severe, toxic symptoms occurred in the 2,190 mg/kg treatment group, but animals were normal within 24 hours following removal of the gauze.

3) $PCPMSO_2$

In an acute, oral toxicity study, Thake *et al.* (1979) gavaged Fischer 344 rats (10/sex/dose, except one male and four female dose groups with 20 rats) with $PCPMSO_2$ dissolved in corn oil and observed the animals twice daily for mortality and toxic symptoms. The dose levels, which ranged from 464 to 708 mg/kg in males and 282 to 473 mg/kg in females, had been established to produce 0-100% mortality. Ten rats/sex served as controls. At all treatment levels in both sexes, there was an immediate decrease in locomotor activity. This was followed, at the higher doses, with a loss of coordination, prostration, diarrhea, loss of consciousness, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within 4 hours in some rats at the highest dose. No toxicity or mortality was observed in controls. The LD_{50}s for $PCPMSO_2$ were higher for males (529 mg/kg) than for females (400 mg/kg) (Table 3).

In a similar, acute gavage study with $B_6C_3F_1$ mice (10/sex/dose, except one female treatment group with 9 mice), Thake *et al.* (1979) administered $PCPMSO_2$ dissolved in corn oil and observed the mice twice daily for mortality and toxic symptoms. The dose levels, which had been established to produce 0-100% mortality, ranged from 562 to 794 mg/kg for both sexes. Ten mice/sex served as controls. At all treatment levels in both sexes, there was an immediate decrease in locomotor activity. This was followed at the higher doses with a loss of coordination, prostration, loss of consciousness, diarrhea, labored respiration, and death. The investigators indicated that dehydration and starvation in prostrate animals may have contributed to the deaths of treated animals, although death occurred within hours in some mice at the highest dose. No toxicity or mortality was observed in controls. The LD_{50}s for $PCPMSO_2$ were 600 mg/kg for males and 606 mg/kg for females (Table 3).

In an acute dermal toxicity study, Thake *et al.* (1979) applied gauze sponges with $PCPMSO_2$ in acetone to the shaved backs of Fischer 344 rats (2/sex/dose) for 24 hours and observed the animals daily for 14 days. The dose levels were 0, 1,000, 2,190, or 5,630 mg/kg. No deaths and no toxic symptoms occurred with this analog.

4) Comparison between PCPMS, PCPMSO, and $PCPMSO_2$

Acute oral doses of PCPMS and PCPMSO were equally toxic to male and female Fischer 344 rats and slightly less toxic than $PCPMSO_2$ to this strain (Thake *et al.*, 1979). However, the investigators reported that while PCPMS and PCPMSO were readily soluble in corn oil, $PCPMSO_2$ was not, and, thus, required higher vehicle volumes, which could have enhanced compound absorption. This effect, however, was not observed in similar experiments with mice. Thake *et al.* (1979) observed in $B_6C_3F_1$ mice that while oral $PCPMSO_2$ was more toxic than PCPMS to male mice, PCPMSO was far more lethal than either $PCPMSO_2$ or PCPMS to both sexes. Thus, while $PCPMSO_2$ was slightly more toxic than PCPMS or PCPMSO when administered orally in rats, mice were more sensitive to the lethal effects of PCPMSO. Severe lacrimation was observed in rats and mice given PCPMS or PCPMSO but not in $PCPMSO_2$ treated animals.

The types of toxic symptoms observed in rats following oral exposure to all three analogs were similar to those observed following dermal applications of PCPMS or PCPMSO. Dermal application of $PCPMSO_2$, however, had no effect. The investigators did not indicate whether $PCPMSO_2$ had been absorbed through the skin.

b. *Primary Irritation, Dermal Sensitization, and Ophthalmologic Effects*

Thake *et al.* (1979) conducted skin irritation studies of PCPMS, PCPMSO, and $PCPMSO_2$ on 18 male and female New Zealand albino rabbits. Three animals/sex/compound were treated with slurries or solutions of the compounds at 50% (w/v) concentrations in corn oil according to the Modified Draize Procedure. The animals' skin was graded and evaluated at 24, 48, and 72 hours post-treatment. The PCPMS analog did not produce irritation in any of the treated rabbits. The $PCPMSO_2$ analog produced a mild irritation in one male and one female, and PCPMSO produced a mild irritation in two males and two females and a severe reaction in one female rabbit.

Background document C, reference 12

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Background Document C, Reference 14

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See Background Document B, Reference 32

Determination of Rate Constants of Hydrolysis by a Distribution Technique and its Application to *iso*Propoxy-methyl-phosphoryl Chloride

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An improved formula [1] for the determination of the distribution constant of a compound reacting with one of the phases according to a first order reaction is given. Based on this formula a method for the study of rapid hydrolyses is described. The application of the method is illustrated by the determination of the rate of the hydrolysis of *iso*propoxy-methyl-phosphoryl chloride, and its relationship to that of the corresponding fluorine derivative (Sarin) is discussed.

In an earlier paper [1] the author has deduced the following formula for the calculation of the distribution constant of a compound which reacts with one of the phases according to a first order or a pseudo-first order reaction:

$$\ln\,[A]_{aq} = -\frac{k \cdot t}{\frac{v_{org}}{v_{aq}}\,k_d + 1} + C \qquad (1)$$

where $[A]_{aq}$ = concentration of unhydrolysed compound in the aqueous phase;
C = integration constant;
k = reaction rate constant of A in water;
k_d = distribution constant of A between organic and aqueous phase;
t = time;
v = phase volume.

By plotting log $[A]_{aq}$ against t a straight line is obtained the slope of which, α, is

$$\alpha = \frac{0.4343\ k}{\frac{v_{org}}{v_{aq}}\,k_d + 1} \qquad (2)$$

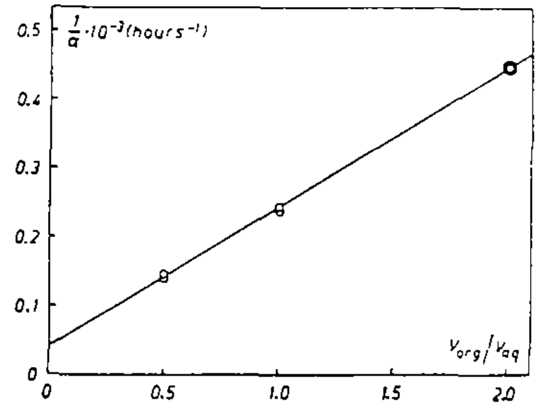

Fig. 1. The reciprocal of the rate of the hydrolysis of 2-methoxy-ethyl nicotinate at various ratios of xylene and water.

The application of the formula was illustrated by the determination of the distribution constant of the ester 2-methoxy-ethyl nicotinate between xylene and water. The rate constant of the hydrolysis was determined in a separate experiment. However, both the rate constant and the distribution constant can be determined simultaneously from a series of experiments where the ratios of the phase volumes are varied. If eqn. (2) is rearranged to

$$\frac{1}{|\alpha|} = \frac{k_d}{0.4343\ k} \cdot \frac{v_{org}}{v_{aq}} + \frac{1}{0.4343\ k} \qquad (3)$$

it appears that a straight line is obtained when $1/|\alpha|$ is plotted against v_{org}/v_{aq}. The rate constant, k, is thus obtained from the intercept of the ordinate and the distribution constant, k_d, from the slope of the line. This is illustrated in Fig. 1 by the example given in the previous paper [1]. As shown in Table 1, k and k_d determined in this way agree well with earlier results.

Table 1. The rate constant of the hydrolysis of 2-methoxy-ethyl nicotinate and its distribution constant between xylene and water.

	According to	
	eqn. (3)	previous paper [1]
k hours^{-1}	5.36×10^{-2}	5.07×10^{-2}
k_d	4.67	4.28

The problem can also be considered as a consecutive reaction *i.e.*:

$$\mathrm{A_{org}} \underset{k_{aq}}{\overset{k_{org}}{\rightleftharpoons}} \mathrm{A_{aq}} \xrightarrow{k_1} \mathrm{P}$$

where P is a hydrolysis product. If this system is treated according to the improved steady-state approximation given by McDaniel and Smoot [2], and $k_{aq}/k_{org} = k_d$, then

$$\ln\,[\mathrm{A}]_{aq} = -\frac{k_1 \cdot t}{\dfrac{v_{org}}{v_{aq}}\left(k_d + \dfrac{k_1}{k_{org}}\right) + 1} + C \tag{4}$$

If $k_{org} \gg k_1$ which is the case in slow reactions, eqn. (4) is reduced to eqn. (1). In rapid reactions none of the constants can be neglected and we get, analogously to eqn. (3)

$$\frac{1}{|\alpha|} = \frac{1}{0.4343}\left(\frac{k_d}{k_1} + \frac{1}{k_{org}}\right) \cdot \frac{v_{org}}{v_{aq}} + \frac{1}{0.4343\ k_1} \tag{5}$$

Obviously from this equation, k_1 can be determined, by plotting $1/|\alpha|$ against v_{org}/v_{aq}; k_d, however, cannot be determined, because it is not possible to estimate k_{org}.

The distribution technique is particularly suitable for studies of rapid hydrolysis. The diminished rate due to the inert phase added permits measurements of reactions which in aqueous solutions run too fast for accurate determinations. The technique was therefore used in the determination of the rate constant of the hydrolysis of *iso*propoxy-methyl-phoshoryl chloride. The study of this hydrolysis forms part of an investigation of the influence of the substituents on the rate of hydrolysis of Sarin analogues [3]. *Iso*propoxy-methyl-phosphoryl chloride is assumed to hydrolyse according to a first-order reaction when the pH is maintained constant, and eqn. (5) is thus valid.

EXPERIMENTAL

Materials: *Iso*propoxy-methyl-phosphoryl chloride was synthesized by reacting methyl-phosphoryl dichloride [4] with *iso*propanol, and was freshly distilled before use. B.p. 51°C/4 mm Hg; n_D^{25} 1.4275; d_4^{25} 1.140.

Chloroform: E. Merck; anal. reagent.

Procedure: The rate of the hydrolysis of *iso*propoxy-methyl-phosphoryl chloride during the distribution between chloroform and a 0.100 M solution of potassium chloride was studied at pH 7.00 and 25.0°C. The pH was maintained constant by means of an automatic recording titrator [4] which was standardized before each run against a 0.05 M solution of potassium hydrogen *o*-phthalate (pH 4.01). A constant temperature, circulating water bath maintained the jacketed reaction vessel at ± 0.1°C or better.

A 0.80 mM stock solution of the compound in dry chloroform was prepared. Experiments were performed with four different ratios of the volumes of chloroform solution to aqueous solution as shown in Table 2. The total volume of each sample was 40 ml.

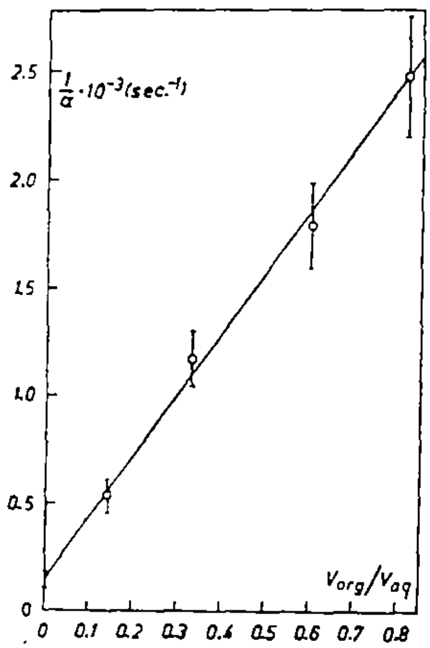

Fig. 2. The reciprocal of the rate of th[e] hydrolysis of *iso*propoxy-methyl-phos[-]phoryl chloride at various ratios of chlo[-]roform and water.

Table 2. Ratio of the volumes of chloroform solution to aqueous solution.

v_{org} / v_{aq}	5 : 35	10 : 30	15 : 25	18 : 22

The aqueous solution was in advance adjusted to the desired pH. The addition of pu[re] chloroform to the aqueous solution has no influence upon pH. Each set of experimen[ts] was repeated five times. Some difficulties arose in getting a suitable speed of the magneti[c] stirrer. Too rapid stirring caused great fluctuations of pH during the run owing to chloro[-]form splashing over the electrodes and shielding them. On the other hand slow stirrin[g] did not permit equilibrium to be attained. With a few exceptions the variations of pH during the runs were $\pm$ 0.1 or less. The products formed in the hydrolysis, hydrochlori[c] acid and *iso*propoxy-methyl-hydroxy-phosphine oxide, are assumed to be completely sol[-]uble in the aqueous phase at the actual pH. The curves obtained were treated accordin[g] to Guggenheim [6]. Straight lines were obtained the slopes of which were calculated. The straight lines indicate that no appreciable association did occur in the chloro[-]form phase [1].

RESULTS AND DISCUSSION

When $1/|a|$ is plotted against v_{org}/v_{aq} for the hydrolysis of *iso*propoxy[-]methyl-phosphoryl chloride in various ratios of chloroform and water a[t] pH 7.00 a straight line is obtained as shown in Fig. 2. The equation of the line was calculated by the method of least squares with weighted values (9:5:2:1). The intercept of the ordinate of the line was found to be (0.151 ±

$0.041) \times 10^3$ which corresponds to a rate constant of the hydrolysis of $(1.5 \pm 0.4) \times 10^{-2}$ sec.$^{-1}$.

If it is assumed that the rate of the hydrolysis of *iso*propoxy-methylphosphoryl chloride is proportional only to the hydroxyl ion concentration as is valid for Sarin [3], the bimolecular rate constant, k_2, would be 1.2×10^5 l mole^{-1} sec.$^{-1}$, *i.e.* 5×10^3 times greater than that of the fluorine derivative (Sarin). Because of the greater electronegativity of fluorine which makes the phosphours atom more electron deficient and positive, the formation of the P-OH bond is facilitated more in the fluorine than in the chlorine compound. By using Pauling's values of electronegativity of P, Cl and F a rough calculation according to Hannay and Smyth [7] shows that the P—F and P—Cl bonds are 43 and 17 % ionic, respectively. If the difference in the ionic character of the bonds is the rate determining factor, one would expect that the fluorine compound would hydrolyse more rapidly than the chlorine compound. The considerably greater hydrolytic stability of the fluorine derivative may, however, be ascribed principally to the higher bond energy of the P—F bond, 120 kcal/mole, in comparison with that of the P—Cl bond, 80 kcal/mole [8].

The author is indebted to Professor G. Ljunggren, Director of this Institute, for the kind interest he has shown in this work. The author wishes also to express his thanks to Fil.lic. K.-E. Almin, Swedish Forest Products Research Laboratory, for valuable discussions.

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Received October 24, 1957.

IPA,
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Hazardous Chemicals Desk Reference

Second Edition

Richard J. Lewis, Sr.

1991

VNR VAN NOSTRAND REINHOLD
New York

ˊA ˏ13-42-8 HR: 2
. CARBINOL

ıw: 72.12

0.852 @ 20°/4°C, bp: 114.5°,

ıLCOHOL (DOT) * 2-METHYL-

ΞPORTS: Reported in EPA

.r Flammable or Combusti-
.:: Flammable Liquid.

:. Moderately toxic by inges-
:. Mildly toxic by inhalation.
ımmable when exposed to
ˑn heated to decomposition
: and fumes.

S: 109-59-1 HR: 2
ΤHANOL
.v: 104.17

ˑT * ETHYLENE GLYCOL
:THYLENE GLYCOL, MONOISO-
ˑD[illegible]YETHYL ISOPROPYL
:I OLVE * ISOPROPYL
ROPYL ETHER of ETHYLENE

ƆRTS: Glycol ether com-
ımmunity Right-To-Know
A TSCA Inventory.

ˆ5 ppm
.5 ppm

Moderately toxic by skin
neal routes. Mildly toxic
:gestion. When heated to
ıts acrid smoke and fumes.

Ƽ: 108-21-4 HR: 2
TATE

.: 102.15

ııatic liquid. Mp: −73°,
. uel: 7.8%, fp: −69.3°,
ɪ 20°/20°, autoign temp:
ˀ mm @ 17.0°, d: 3.52.
.e in alc, ether, fixed oils.

ROPYLE (FRENCH) * ACE-
R * ACETIC ACID-I-

METHYLETHYL ESTER (9CI) * 2-ACETOXYPROPANE * FEMA No. 2926 * ISOPROPILE (ACETATO di) (ITALIAN) * ISOPROPYLACETAAT (DUTCH) * ISOPROPYLACETAT (GERMAN) * ISOPROPYL (ACETATE d') (FRENCH) * 2-PROPYL ACETATE

CONSENSUS REPORTS: Reported in EPA TSCA Inventory.

OSHA PEL: (Transitional: TWA 250 ppm) TWA 250 ppm; STEL 310 ppm
ACGIH TLV: TWA 250 ppm; STEL 310 ppm
DFG MAK: 200 ppm (840 mg/m^3)
DOT Classification: Flammable Liquid; Label: Flammable Liquid.

SAFETY PROFILE: Moderately toxic by ingestion. Mildly toxic by inhalation. Human systemic irritant effects by inhalation and systemic eye effects by an unspecified route. Narcotic in high concentration. Chronic exposure can cause liver damage. Highly flammable liquid. Dangerous fire hazard when exposed to heat, flame, or oxidizers. Moderately explosive when exposed to heat or flame. Dangerous; keep away from heat and open flame; can react vigorously with oxidizing materials. To fight fire, use foam, CO_2, dry chemical.

INJ000 CAS: 67-63-0 **HR: 3**
ISOPROPYL ALCOHOL

DOT: UN 1219
mf: C_3H_8O mw: 60.11

PROP: Clear, colorless liquid; slt odor, sltly bitter taste. Mp: −88.5 to −89.5°, bp: 82.5°, lel: 2.5%, uel: 12%, flash p: 53°F (CC), d: 0.7854 @ 20°/4°, refr index: 1.377 @ 20°, vap d: 2.07, ULC: 70. fp: −89.5°; autoign temp: 852°F. Misc with water, alc, ether, chloroform; insol in salt solns.

SYNS: ALCOOL ISOPROPILICO (ITALIAN) * ALCOOL ISOPROPYLIQUE (FRENCH) * DIMETHYLCARBINOL * ISOHOL * ISOPROPANOL (DOT) * ISOPROPYLALKOHOL (GERMAN) * LUTOSOL * PETROHOL * PROPAN-2-OL * 2-PROPANOL * i-PROPANOL (GERMAN) * sec-PROPYL ALCOHOL (DOT) * i-PROPYLALKOHOL (GERMAN) * SPECTRAR

CONSENSUS REPORTS. IARC Cancer Review: GROUP 3 IMEMDT 7,229,87. The isopropyl alcohol strong acid manufacturing process is on the Community Right-To-Know List. EPA Genetic Toxicology Program. Reported in EPA TSCA Inventory.

OSHA PEL: (Transitional: TWA 400 ppm) TWA 400 ppm; STEL 500 ppm
ACGIH TLV: TWA 400 ppm; STEL 500 ppm
DFG MAK: 400 ppm (980 mg/m^3)
NIOSH REL: (Isopropyl Alcohol) TWA 400 ppm; CL 800 ppm/15M
DOT Classification: Flammable Liquid; Label: Flammable Liquid.

SAFETY PROFILE: Poison by ingestion and subcutaneous routes. Moderately toxic to humans by an unspecified route. Moderately toxic experimentally by intravenous and intraperitoneal routes. Mildly toxic by skin contact. Human systemic effects by ingestion or inhalation: flushing, pulse rate decrease, blood pressure lowering, anesthesia, narcosis, headache, dizziness, mental depression, hallucinations, distorted perceptions, dyspnea, respiratory depression, nausea or vomiting, coma. Experimental teratogenic and reproductive effects. Questionable carcinogen. Mutation data reported. An eye and skin irritant.

The single lethal dose for a human adult is about 250 mL although as little as 100 mL can be fatal. It can cause corneal burns and eye damage. Acts as a local respiratory irritant and in high concentration as a narcotic. It has good warning properties because it causes a mild irritation of the eyes, nose, and throat at a concentration level of 400 ppm. It may induce a mild narcosis, the effects of which are usually transient, and it is somewhat less toxic than the normal isomer, but twice as volatile.

There is some evidence that humans can acquire a slight tolerance to this material. It is absorbed by the skin, but single or repeated applications on the skin of rats, rabbits, dogs, or human beings induced no untoward effects. It acts very much like ethanol in regard to absorption, metabolism, and elimination but with a stronger narcotic action. Chronic injuries have been detected in animals. Workers producing isopropanol show an excess of sinus and laryngeal cancers. This may all or in part be due to the by-product, isopropyl oil. Humans have ingested up to 20 mL diluted with water and noticed only a sensation of heat and slight lowering of the blood pressure. There are, however, reports of serious illness from as little as 10 mL taken internally. A common air contaminant.

Flammable liquid. A very dangerous fire hazard when exposed to heat, flame, or oxidizers. Moderately explosive when exposed to heat or flame. Reacts with air to form dangerous peroxides. The presence of 2-butanone increases the reaction rate for peroxide formation. Hydrogen peroxide sharply reduces the autoignition temperature. Violent explosive reaction when heated with aluminum isopropoxide + crotonaldehyde + heat. Forms explosive mixtures with trinitromethane, hydrogen peroxide (similar in power and sensitivity to glyceryl nitrate). Reacts with barium perchlorate to form the highly explosive propyl perchlorate. Ignites on contact with dioxygenyl tetrafluoroborate, chromium trioxide, potassium tert-butoxide (after a delay). Reacts with oxygen to form dangerously unstable peroxides. Vigorous reaction with sodium dichromate + sulfuric acid, aluminum (after a delay period). Reacts violently with H_2 + Pd, nitroform, oleum, $COCl_2$, Al triisopropoxide, oxidants. Can react vigorously with oxidizing materials. To fight fire, use CO_2, dry chemical, alcohol foam. When heated to decomposition it emits acrid smoke and fumes.

INK000 CAS: 75-31-0 **HR: 3**
ISOPROPYLAMINE

DOT: UN 1221
mf: C_3H_9N mw: 59.13

PROP: Colorless liquid, amino odor. Mp: −101.2°, flash p: −35°F (OC), d: 0.694 @ 15°/4°, autoign temp: 756°F, d: 2.03, bp: 33-34°, lel: 2.3%, uel: 10.4%; misc with H_2O, alc, ether.

SYNS: 2-AMINO-PROPAAN (DUTCH) * 2-AMINO-PROPAN (GERMAN) * 2-AMINOPROPANE * 2-AMINO-PROPANO (ITALIAN) * ISOPROPILAMINA (ITALIAN) * 1-METHYLETHYLAMINE * MONOISOPROPYLAMINE * 2-PROPANAMINE * sec-PROPYLAMINE * 2-PROPYLAMINE

CONSENSUS REPORTS: Reported in EPA TSCA Inventory.

OSHA PEL: (Transitional: TWA 5 ppm) TWA 5 ppm; STEL 10 ppm
ACGIH TLV: TWA 5 ppm; STEL 10 ppm
DFG MAK: 5 ppm (12 mg/m³)
DOT Classification: Flammable Liquid; Label: Flammable Liquid.

SAFETY PROFILE: Poison by skin contact. Moderately toxic by ingestion and possibly other routes. Mildly toxic by inhalation. A severe skin and eye irritant. Occasionally contact causes sensitization. Narcotic in high concentration. Very dangerous fire hazard and moderate explosion hazard when exposed to sparks, heat, flame or oxidizers. Can react vigorously with oxidizing materials. Reacts with perchloryl fluoride to form an explosive liquid. Incompatible with 1-chloro-1,3-epoxypropane. To fight fire, use alcohol foam, foam, CO_2, dry chemical. When heated to decomposition it emits toxic fumes of NO_x.

INT000 CAS: 51-02-5 **HR: 3**
α-((ISOPROPYLAMINO)METHYL) NAPHTHALENEMETHANOL, HYDROCHLORIDE
mf: $C_{15}H_{19}NO_2 \cdot ClH$ mw: 265.81

SYNS: ALDERLIN HYDROCHLORIDE * ICI 38174 * I.C.I. HYDROCHLORIDE * INETOL * 2-ISOPROPYLAMINO-1-(2-NAPHTHYL)ETHANOL HYDROCHLORIDE * α-(((1-METHYLETHYL)AMINO)METHYL)-2-NAPHTHALENEMETHANOL, HYDROCHLORIDE * NAPHTHYLISOPROTERENOL HYDROCHLORIDE * NETHALIDE HYDROCHLORIDE * PRONETHALOL * PRONETHALOL HYDROCHLORIDE

CONSENSUS REPORTS: IARC Cancer Review: GROUP 3 IMEMDT 7,56,87; Animal Limited Evidence IMEMDT 13,227,77.

SAFETY PROFILE: A poison by intravenous and intraperitoneal routes. Moderately toxic by ingestion. Questionable carcinogen with experimental tumorigenic data. When heated to decomposition it emits very toxic fumes of NO_x and HCl.

INW000 CAS: 63710-43-0 **HR: 3**
9-((3-(ISOPROPYLAMINO)PROPYL) AMINO)-1-NITROACRIDINE DIHYDROCHLORIDE
mf: $C_{19}H_{22}N_4O_2 \cdot 2ClH$ mw: 411.37

SYNS: N-(1-METHYLETHYL)-N'-(1-NITRO-9-ACRIDINYL)-1,3-PROPANEDIAMINE DIHYDROCHLORIDE * 1-NITRO-9-(3-ISOPROPYLAMINOPROPYLAMINE)-ACRIDINE DIHYDROCHLORIDE * 1-NITRO-9-(3-ISOPROPYLAMINOPROPYLAMINO)-ACRIDINE DIHYDROCHLORIDE

CONSENSUS REPORTS: EPA Genetic Toxicology Program.

SAFETY PROFILE: A poison by ingestion and intravenous routes. Human mutation data reported. When heated to decomposition it emits very toxic fumes of NO_x and HCl.

INX000
N-ISOPROPYL
mf: $C_9H_{13}N$
SYNS: o-AMINOIS
ISOPROPYLBENZENE
PROPYLANILINE *
METHYLETHYLBEN
CONSENSUS F
TSCA Inventory.
OSHA PEL: TW
ACGIH TLV: TW
SAFETY PROFIL
tion. When heate
toxic fumes of N(

INY000 (
4-ISOPROPYLA
mf: $C_{14}H_{18}N_2O$
SYNS: 1,2-DIHYDRC
ETHYL)AMINO)-2-PHE
* ISOPROPYLANTIPY
* 4-ISOPROPYL-2,3-D
LIN-5-ONE * ISOPR
* LARODON * 1-P
PYL-3-PYRAZOLIN-5-O
4-ISOPROPYLPYRAZOL
CONSENSUS R
TSCA Inventory.
SAFETY PROFIL
intraperitoneal rou
position it emits to

INZ000 CA
5-ISOPROPYL-1
mf: $C_{21}H_{18}$ m
SYN: 8-ISOPROPYLBE
SAFETY PROFIL
with experimental
heated to decomp
and fumes.

IOB000 C
ISOPROPYLBEN
HYDROPEROXI
DOT: UN 2116
mf: $C_9H_{12}O_2$ r
PROP: Bp: 153°,
hydroperoxide of c
SYNS: CUMEENHYD
* CUMENE HYDROPE

PGT250 CAS: 24928-17-4 **HR: 2**
PHORBOL-12,13-DIDECANOATE
mf: $C_{40}H_{55}O_8$ mw: 663.95

SYN: PDD

SAFETY PROFILE: A skin irritant. Questionable carcinogen with experimental tumorigenic data. Mutation data reported. When heated to decomposition it emits acrid smoke and irritating fumes.

PGV000 CAS: 16561-29-8 **HR: 3**
PHORBOL MYRISTATE ACETATE
mf: $C_{36}H_{56}O_8$ mw: 616.92

SYNS: PENTAHYDROXY-TIGLIADIENONE-MONOACETATE(C)MONOMYRISTATE(B) * PHORBOL ACETATE, MYRISTATE * PHORBOL MONOACETATE MONOMYRISTATE * PMA * 12-TETRADECANOYLPHORBOL-13-ACETATE * 12-o-TETRADEKANOYLPHORBOL-13-ACETAT (GERMAN) * TPA

CONSENSUS REPORTS: EPA Genetic Toxicology Program.

SAFETY PROFILE: Deadly poison by intravenous route. Experimental reproductive effects. Human mutation data reported. A skin irritant. Questionable carcinogen with experimental carcinogenic, neoplastigenic, and tumorigenic data. When heated to decomposition it emits acrid smoke and irritating fumes.

PGV500 CAS: 56937-68-9 **HR: 1**
PHORBOLOL MYRISTATE ACETATE
mf: $C_{36}H_{58}O_8$ mw: 618.94

SYNS: PHORBOLOL ACETATE MYRISTATE * TPA-3-β-OL

SAFETY PROFILE: A skin irritant. When heated to decomposition it emits acrid smoke and irritating fumes.

PGV750 CAS: 37415-55-7 **HR: 3**
PHORBOL-12-o-TIGLYL-13-BUTYRATE
mf: $C_{28}H_{40}O_8$ mw: 504.68

SYN: 12-o-TIGLYL-PHORBOL-13-BUTYRATE

SAFETY PROFILE: A skin irritant. Questionable carcinogen with experimental tumorigenic data. When heated to decomposition it emits acrid smoke and irritating fumes.

PGW250 CAS: 504-20-1 **HR: 2**
PHORONE
mf: $C_9H_{14}O$ mw: 138.23

PROP: Solid or greenish liquid. Mp: 28°, flash p: 185°F (OC), d: 0.879, vap press: 1 mm @ 42.0°, vap d: 4.8, bp: 198-199°. Sol in water, alc, and ether.

SYNS: DIISOPROPYLIDENE ACETONE * sym-DIISOPROPYLIDENE ACETONE * 2,6-DIMETHYL-2,5-HEPTADIEN-4-ONE * PHORON (GERMAN)

CONSENSUS REPORTS: Reported in EPA TSCA Inventory.

SAFETY PROFILE: Moderately toxic by subcutaneous route. Flammable when exposed to heat or flame; can react with oxidizing materials. To fight fire, use foam, CO_2, dry chemical. When heated to decomposition it emits acrid smoke and irritating fumes.

PGW750 CAS: 947-02-4 **HR: 3**
PHOSFOLAN
mf: $C_7H_{14}NO_3PS_2$ mw: 255.31

SYNS: AC 47031 * AMERICAN CYANAMID 47031 * C.I. 47031 * CYCLIC ETHYLENE(DIETHOXYPHOSPHINOTHIOYL)DITHIOIMIDOCARBONATE * CYCLIC ETHYLENE P,P-DIETHYL PHOSPHONODITHIOIMIDOCARBONATE * CYLAN * CYOLANE * CYOLANE INSECTICIDE * (DIETHOXYPHOSPHINYL)DITHIOIMIDOCARBONIC ACID CYCLIC ETHYLENE ESTER * 2-(DIETHOXYPHOSPHINYLIMINO)-1,3-DITHIOLANE * P,P-DIETHYL CYCLIC ETHYLENE ESTER OF PHOSPHONODITHIOIMIDOCARBONIC ACID * EI 47031 * ENT 25,830 * 1,2-ETHANEDITHIOL, CYCLIC ESTER with P,P-DIETHYL PHOSPHONODITHIOIMIDOCARBONATE * 1,2-ETHANEDITHIOL, CYCLIC S,S-ESTER with PHOSPHONODITHIOIMIDOCARBONIC ACID P,P-DIETHYL ESTER

CONSENSUS REPORTS: EPA Extremely Hazardous Substances List. Reported in EPA TSCA Inventory.

SAFETY PROFILE: Poison by ingestion and skin contact. An insecticide used against leaf-feeding larvae of cotton insect pests. When heated to decomposition it emits very toxic fumes of PO_x, SO_x, and NO_x.

PGX000 CAS: 75-44-5 **HR: 3**
PHOSGENE

DOT: UN 1076
mf: CCl_2O mw: 98.91

PROP: Colorless, poison gas or volatile liquid; odor of new mown hay or green corn. Mp: −118°, bp: 8.3°, d: 1.37 @ 20°, vap press:

1180 mm @ 20°,
water: very sol in
comp sltly in wate

SYNS: CARBONE (O
* CARBONIO (OSSICL
BON OXYCHLORIDE
MAN) * CARBONYL
CHLORIDE * DIPHOS
* FOSGEN (POLISH)
* KOOLSTOFOXYCHL
* PHOSGEN (GERMAN
P095

CONSENSUS RE
Hazardous Substanc
To-Know List. Rep
tory.

OSHA PEL: TWA
ACGIH TLV: TWA
DFG MAK: 0.1 ppm
NIOSH REL: TWA
DOT Classification
Gas.

SAFETY PROFILE:
tion. A severe eye, sk
irritant. In the preser
decomposes to form
bon monoxide. This
and alveoli of the lun
edema followed by b
casionally lung absce
ate irritating effect u
and the warning prop
fore very slight. The
warning that dangerou
inhaled. After a laten
the patient complains
and chest, shortness
dyspnea. Where the e
the development of p
so rapid that the pati
after exposure. In case
been less, pneumonia
after the occurrence o
who recover, no pern
is thought to occur. A
Under the approp
goes hazardous react
azido formate, 2,4-hex
alcohol, K, Na, sodiu
propylideneamino li
heated to decompositio
or steam it will react to

h liquid. Mp: 28°, flash 9. vap press: 1 mm @ 98-199°. Sol in water,

ACETONE * sym-DIISO- 6-DIMETHYL-2,5-HEPTA- RMAN)

TS: Reported in EPA

erately toxic by subcu- e when exposed to heat th oxidizing materials. , CO_2, dry chemical. position it emits acrid nes.

47-02-4 **HR: 3**

w: 255.31

CAN CYANAMID 47031 YLENE(DIETHOXYPHOS- RBONATE * CYCLIC PHONODITHIOIMIDO- CYOLANE * CYO- IOSPHINYL)DI- CL... ETHYLENE ESTER MINO)-1,3-DITHIOLANE ENE ESTER OF PHOS- ACID * EI 47031 DITHIOL, CYCLIC HONODITHIOIMIDO- ITHIOL, CYCLIC HIOIMIDOCARBONIC

TS: EPA Extremely ist. Reported in EPA

son by ingestion and de used against leaf- insect pests. When n it emits very toxic NO_x.

5-44-5 **HR: 3**

l

s or volatile liquid; or green corn. Mp: 20°, vap press:

1180 mm @ 20°, vap d: 3.4. Very sltly sol in water; very sol in benzene and acetic acid; decomp sltly in water.

SYNS: CARBONE (OXYCHLORURE de) (FRENCH) * CARBONIO (OSSICLORURO di) (ITALIAN) * CARBON OXYCHLORIDE * CARBONYLCHLORID (GERMAN) * CARBONYL CHLORIDE * CHLOROFORMYL CHLORIDE * DIPHOSGENE * FOSGEEN (DUTCH) * FOSGEN (POLISH) * FOSGENE (ITALIAN) * KOOLSTOFOXYCHLORIDE (DUTCH) * NCI-C60219 * PHOSGEN (GERMAN) * RCRA WASTE NUMBER P095

CONSENSUS REPORTS: EPA Extremely Hazardous Substances List. Community Right-To-Know List. Reported in EPA TSCA Inventory.

OSHA PEL: TWA 0.1 ppm
ACGIH TLV: TWA 0.1 ppm
DFG MAK: 0.1 ppm (0.4 mg/m^3)
NIOSH REL: TWA 0.1 ppm; CL 0.2 ppm/15M
DOT Classification: Poison A; Label: Poison Gas.

SAFETY PROFILE: A human poison by inhalation. A severe eye, skin, and mucous membrane irritant. In the presence of moisture, phosgene decomposes to form hydrochloric acid and carbon monoxide. This occurs in the bronchioles and alveoli of the lungs resulting in pulmonary edema followed by bronchopneumonia and occasionally lung abscess. There is little immediate irritating effect upon the respiratory tract, and the warning properties of the gas are therefore very slight. There may be no immediate warning that dangerous concentrations are being inhaled. After a latent period of 2 to 24 hours, the patient complains of burning in the throat and chest, shortness of breath and increasing dyspnea. Where the exposure has been severe, the development of pulmonary edema may be so rapid that the patient dies within 36 hours after exposure. In cases where the exposure has been less, pneumonia may develop several days after the occurrence of the accident. In patients who recover, no permanent residual disability is thought to occur. A common air contaminant.

Under the appropriate conditions it undergoes hazardous reactions with Al, tert-butyl azido formate, 2,4-hexadiyn-1,6-diol, isopropyl alcohol, K, Na, sodium azide, hexafluoroisopropylideneamino lithium, lithium. When heated to decomposition or on contact with water or steam it will react to produce toxic and corrosive fumes of Cl^-. Caution: Arrangements should be made for monitoring its use.

PGX500 **HR: 2**
PHOSPHATES

SAFETY PROFILE: Alkali metal phosphates are strong caustics and therefore powerful irritants. Superphosphate is $Ca(H_2PO_4)_2/CaSO_4$. Triple superphosphate contains P_2O_5. Both are used as fertilizers. Organophosphates are often highly toxic pesticides. For an example of organic phosphates, see PARATHION.

PGX750 **HR: 3**
PHOSPHIDES

PROP: A combination of a cation + elemental phosphorus.

SAFETY PROFILE: Phosphides are particularly dangerous because they tend to decompose to the very toxic phosphine upon contact with moisture or acids. Dangerous fire hazard by chemical reaction, particularly with moisture. Moderate explosion hazard. They react with water, steam, acid, or acid fumes to produce toxic and flammable phosphine gas. Can react vigorously with oxidizing materials. Dangerous; when heated to decomposition they may emit highly toxic fumes of PO_x.

PGY000 CAS: 7803-51-2 **HR: 3**
PHOSPHINE

DOT: UN 2199
mf: H_3P mw: 34.00

PROP: Colorless gas; foul odor of decaying fish. Mp: −132.5°, bp: −87.5°, d: 1.529 g/L @ 0°, autoign temp: 212°F, lel: 1%. Sltly sol in water.

SYNS: CELPHOS * DELICIA * DETIA GAS EX-B * FOSFOROWODOR (POLISH) * HYDROGEN PHOSPHIDE * PHOSPHORUS TRIHYDRIDE * PHOSPHORWASSERSTOFF (GERMAN) * RCRA WASTE NUMBER P096

CONSENSUS REPORTS: EPA Extremely Hazardous Substances List. Reported in EPA TSCA Inventory.

OSHA PEL: (Transitional: TWA 0.3 ppm) TWA 0.3 ppm; STEL 1 ppm
ACGIH TLV: TWA 0.3 ppm; STEL 1 ppm
DFG MAK: 0.1 ppm (0.15 mg/m^3)
DOT Classification: Poison A; Label: Flammable Gas and Poison Gas.

Background Document C, Reference 17

Lyman, W.J., et al., 1990, *Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds*, American Chemical Society, Washington, D.C.

See Background Document B, Reference 36

Background Document C, Reference 18

Major, M.A., 1989, *Octanol/Water Partition Coefficients of Surface and Ground Water Contaminants Found at Military Installations*, Technical Report 88-10, U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, Md., Nov.

See Background Document B, Reference 38

DELIST\DIMPMEMO.MAJ

MEMORANDUM FOR RECORD

PERSONAL COMMUNICATION WITH: Dr. Michael A. Major, Chemist
U.S. Army Biomedical Research and Development Laboratory
Fort Detrick, Frederick, MD

BY: David H. Rosenblatt, Argonne National Laboratory, Argonne, Illinois

SUBJECT: Miscibility of DIMP (Diisopropyl Methylphosphonate) with Water

DATE: 4 December 1990.

Responding to a request for information from the undersigned, Dr. Major performed a quick room-temperature experiment, titrating water with DIMP (with stirring). He reached the conclusion that DIMP is infinitely soluble in water.

David H. Rosenblatt, Ph.D.

2-CHLOROACETOPHENONE

DIALOG Bluesheets

Last Loaded On Web: July 11, 1997 1:42AM PST
Last Update To Bluesheet: April 30, 1997

REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS) [336]

Blue Sheet Indexes:	Database Name	File Number	Subject	OneSearch	Search Options
Blue Sheets By File Number:	Previous	List	Next		

- ## Blue Sheet Contents

Top	File Description	Subject Coverage	Sources	Print Counterparts	Dialog File Data	Database Content	Document Types Indexed
Geographic Coverage	Special Features	DIALINDEX/OneSearch Acronyms	Origin	Terms and Conditions	Basic Index	Additional Indexes	Notes
Limiting	Sorting	Format Options	Printed Blue Sheet Status	OnLine Blue Sheet Status	Rates	Sample Record	

- ## File Description

The Registry of Toxic Effects of Chemical Substances (RTECS) is a comprehensive database of basic toxicity information for over 100,000 chemical substances including: prescription and non-prescription drugs, food additives, pesticides, fungicides, herbicides, solvents, diluents, chemical wastes, reaction products of chemical waste, and substances used in both industrial and household situations. Reports of the toxic effects of each compound are cited. In addition to toxic effects and general toxicology reviews, data on skin and/or eye irritation, mutation, reproductive consequences and tumorigenicity are provided. Federal standards and regulations, NIOSH recommended exposure limits and information on the activities of the EPA, NIOSH, NTP, and OSHA regarding the substance are also included. The toxic effects are linked to literature citations from both published and unpublished governmental reports, and published articles from the scientific literature. The database corresponds to the print version of the Registry of Toxic Effects of Chemical Substances, formerly known as the Toxic Substances List started in 1971, and is prepared by the National Institute for Occupational Safety and Health (NIOSH).

Toxicity information appearing in RTECS is derived form reports of acute, chronic, lethal and non-lethal effects of chemical substances. The reviewed information from the scientific literature and published governmental reports plus unpublished test data from the EPA TSCA test submissions database (TSCATS) are included in the file.

- ## Subject Coverage

  - Chemical Identity and Class
  - Irritation Data
  - Mutation Data
  - NIOSH Criteria Documents
  - NTP, NIOSH, and EPA Status

   - Reproductive Effects Data
   - Standards and Regulations
   - Toxicology Reviews
   - Tumorigenic Effects Data

- **Sources**

  Toxicity information appearing in RTECS is derived from reports of acute, chronic, lethal and non-lethal effects of chemical substances. The reviewed information from the scientific literature and published governmental reports plus unpublished test data from the EPA TSCA test submissions database (TSCATS) are included in the file.

- **Print Counterparts**

   - Registry of Toxic Effects of Chemical Substances

- **Dialog File Data**

  Dates Covered:
  June 1971 to the present
  File Size:
  More than 138,000 records as of April 1997
  Update Frequency:
  Quarterly

- **Database Content**

   - Directories

- **Document Types Indexed**

   - Government Documents
   - Journal Articles

- **Geographic Coverage**

   - International

- **Special Features**

   - Classroom Instruction Program
   - KWIC and HILIGHT available
   - MAP available

- **DIALINDEX/OneSearch Acronyms**

Acronym	Previous File	Next File
CASREGNO	MATERIAL SAFETY LABEL DATA - OHS [334]	CHEMTOX(R) ONLINE [337]
CHEMREGS	MATERIAL SAFETY LABEL DATA - OHS [334]	CHEMTOX(R) ONLINE [337]
ENERGREG	MATERIAL SAFETY SUMMARY SHEETS - OHS [333]	CHEMTOX(R) ONLINE [337]
REGS	MATERIAL SAFETY SUMMARY SHEETS - OHS [333]	CHEMTOX(R) ONLINE [337]
RNCHEM	MATERIAL SAFETY LABEL DATA - OHS [334]	CHEMTOX(R) ONLINE [337]
RNMED	PESTICIDE FACT FILE [306]	DERWENT DRUG REGISTRY FILE [375]
SAFETY	MATERIAL SAFETY LABEL DATA - OHS [334]	CHEMTOX(R) ONLINE [337]
TOXICOL	MATERIAL SAFETY DATA SHEETS - OHS [332]	CHEMTOX(R) ONLINE [337]

- **Origin**

Department of Health and Human Services
Public Health Service, Center for Disease Control
National Institute for Occupational Safety and Health
4676 Columbia Parkway
Cincinnati
OH
45226

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- **Search Options**

For 97-0567
DR. DAVID ROSENBLATT

b 336

15jul97 09:34:57 User201147 Session D143.1
$0.09 0.003 Hrs File1
$0.09 Estimated cost File1
$0.01 INTERNET
$0.10 Estimated cost this search
$0.10 Estimated total session cost 0.003 Hrs.

File 336:RTECS 1997/Q2

Set	Items	Description

?s rn=532-27-4

S1	1	RN=532-27-4

?d s1/9/all

Display 1/9/1
DIALOG(R)File 336:RTECS

006221 RTECS Number: AM6300000
Substance Name: Acetophenone, 2-chloro-
CAS Registry Number: 532-27-4 Molecular Formula: C8H7ClO
Molecular Weight: 154.60 Beilstein Registry Number: 507950
Beilstein Source Citation: 4-07-00-00641
Synonyms: Chemical mace ; Chloracetophenone ; alpha-Chloroacetophenone ; omega-Chloroacetophenone ; 2-Chloroacetophenone ; alpha-Chloroacetophenone (ACGIH:OSHA) ; Chloroacetophenone, liquid or solid (DOT) ; Chloromethyl phenyl ketone ; 2-Chloro-1-phenylethanone ; CN ; CN, liquid or solid (DOT) ; Ethanone, 2-chloro-1-phenyl- ; Mace (lacrimator) ; NCI-C55107 ; Phenacyl chloride (OSHA) ; Phenylchloromethylketone ; UN1697 (DOT)
Compound Class: Tumorigen; Mutagen; Human Data; Primary Irritant
Wiswesser Line Notation: G1VR
Record Date: 9704
IRRITATION DATA:
Skin Rat 12 %/6H open Moderate ARTODN 40,75,78
Skin Rabbit 5 mg/24H Mild TXAPA9 17,295,70
Skin Rabbit 12 %/6H open Moderate ARTODN 40,75,78
Eye Rabbit 1 mg Mild TXAPA9 17,295,70
Eye Rabbit 3 mg Severe TXAPA9 17,295,70
Skin Guinea pig 12 %/6H open Moderate ARTODN 40,75,78

MUTATION DATA:
DNA damage Rat Liver 10 umol/L MUREAV 368,59,96
Cytogenetic analysis Hamster Ovary 3 mg/L NTPTR* NTP-TR-379,90

TUMORIGENIC EFFECTS DATA:
Equivocal tumorigenic agent by RTECS criteria ; Endocrine--Tumors ; Skin and appendages--Tumors ; Inhalation Rat TCLo 2 mg/m3/6H/2Y-I

NTPTR* NTP-TR-379,90
Neoplastic by RTECS criteria ; Skin and appendages--Tumors ; Tumors at site of application ; Skin Mouse TDLo 2400 mg/kg/27W-I BJCAAI 7,482,53

TOXICITY EFFECTS DATA:
* Inhalation Human LCLo 159 mg/m3/20M 34ZIAG -,163,69
Lacrimation ;Conjunctive irritation ;Dyspnea Inhalation Human TCLo 93 mg/m3/3M AIHAAP 23,199,62
Eye--Other ;Cough ;Dyspnea Inhalation Human TCLo 20 mg/m3 BJIMAG 29,298,72
* Oral Rat LD50 50 mg/kg TXAPA9 17,295,70
Olfaction--Other ;Acute pulmonary edema ;Hemorrhage Inhalation Rat LCLo 417 mg/m3/15M ARTODN 40,75,78
Coma ;Lungs, Thorax, or Respiration--Other changes ;Hair Intraperitoneal Rat LD50 36 mg/kg ARTODN 40,75,78
Convulsions or effect on seizure threshold ;Respiratory stimulation ;Kidney, Ureter, Bladder--Other changes Intravenous Rat LD50 41 mg/kg ARTODN 40,75,78
* Oral Mouse LD50 139 mg/kg NTIS** AD837-111
* Inhalation Mouse LC50 59 mg/m3 GISAAA 58(10),4,93
* Intraperitoneal Mouse LD50 60 mg/kg NTIS** AD837-111
Convulsions or effect on seizure threshold ;Respiratory stimulation ;Kidney, Ureter, Bladder--Other changes Intravenous Mouse LD50 81 mg/kg ARTODN 40,75,78
Coma ;Lungs, Thorax, or Respiration--Other changes ;Hair Oral Rabbit LD50 118 mg/kg ARTODN 40,75,78
Olfaction--Other ;Acute pulmonary edema ;Hemorrhage Inhalation Rabbit LCLo 465 mg/m3/20M ARTODN 40,75,78
Convulsions or effect on seizure threshold ;Respiratory stimulation ;Kidney, Ureter, Bladder--Other changes Intravenous Rabbit LD50 30 mg/kg ARTODN 40,75,78
Coma ;Lungs, Thorax, or Respiration--Other changes ;Hair Oral Guinea pig LD50 158 mg/kg ARTODN 40,75,78
Olfaction--Other ;Acute pulmonary edema ;Hemorrhage Inhalation Guinea pig LCLo 490 mg/m3/30M ARTODN 40,75,78
Coma ;Lungs, Thorax, or Respiration--Other changes ;Hair Intraperitoneal Guinea pig LD50 17 mg/kg ARTODN 40,75,78

OTHER MULTIPLE DOSE EFFECTS DATA:
Death in the "U" date type field ; Inhalation Rat TCLo 19 mg/m3/6H/14D-I NTPTR* NTP-TR-379,90
Death in the "U" date type field ; Inhalation Mouse TCLo 10 mg/m3/6H/14D-I NTPTR* NTP-TR-379,90

REVIEWS:
ACGIH TLV-Not classifiable as a human carcinogen DTLVS* TLV/BEI,96
ACGIH TLV-TWA 0.32 mg/m3 (0.05 ppm) DTLVS* TLV/BEI,96

STANDARDS AND REGULATIONS:
DOT-HAZARD 6.1; LABEL:POISON CFRGBR 49,172.101,92
MSHA STANDARD-air TWA 0.05 ppm (0.3 mg/m3) DTLVS* 3,48,71
OSHA PEL (Gen Indu) 8H TWA 0.05 ppm (0.3 mg/m3) CFRGBR 29,1910.1000,94
OSHA PEL (Construc) 8H TWA 0.05 ppm (0.3 mg/m3) CFRGBR 29,1926.55,94
OSHA PEL (Shipyard) 8H TWA 0.05 ppm (0.3 mg/m3) CFRGBR 29,1915.1000,93
OSHA PEL (Fed Cont) 8H TWA 0.05 ppm (0.3 mg/m3) CFRGBR 41,50-204.50,94
OEL-AUSTRALIA TWA 0.05 ppm (0.3 mg/m3) JAN93

OEL-BELGIUM TWA 0.05 ppm (0.32 mg/m3) JAN93
OEL-DENMARK TWA 0.05 ppm (0.3 mg/m3) JAN93
OEL-FINLAND STEL 0.05 ppm (0.3 mg/m3);Skin JAN93
OEL-FRANCE TWA 0.05 ppm (0.3 mg/m3) JAN93
OEL-THE NETHERLANDS TWA 0.05 ppm (0.3 mg/m3) JAN93
OEL-THE PHILIPPINES TWA 0.05 ppm (0.3 mg/m3) JAN93
OEL-SWITZERLAND TWA 0.05 ppm (0.3 mg/m3) JAN93
OEL-UNITED KINGDOM TWA 0.05 ppm (0.3 mg/m3) JAN93
OEL IN BULGARIA COLOMBIA, JORDAN, KOREA check ACGIH TLV
OEL IN NEW ZEALAND SINGAPORE, VIETNAM check ACGIH TLV

NIOSH CRITERIA DOCUMENTS:
NIOSH REL TO alpha CHLOROACETOPHENONE-air:10H TWA 0.05 ppm NIOSH* DHHS #92-100,92
NOES 1983: HZD X4754; NIS 1; TNF 35; NOS 4; TNE 2294; TFE 1412

NTP, NIOSH, EPA STATUS:
EPA TSCA Section 8(b) CHEMICAL INVENTORY
EPA TSCA Section 8(d) unpublished health/safety studies
On EPA IRIS database
EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, APRIL 1997
NTP Carcinogenesis Studies (inhalation);equivocal evidence:rat NTPTR* NTP-TR-379,90
NTP Carcinogenesis Studies (inhalation);no evidence:mouse NTPTR* NTP-TR-379,90

IRRITATION EFFECTS JOURNAL REFERENCES:
ARTODN Archives of Toxicology. Springer-Verlag, Heidelberger Pl. 3, D-1000 Berlin 33, Fed. Rep. Ger. V.32- 1974-
TXAPA9 Toxicology and Applied Pharmacology. Academic Press, Inc., 1 E. First St., Duluth, MN 55802 V.1- 1959-

MUTATION EFFECTS JOURNAL REFERENCES:
MUREAV Mutation Research. Elsevier Science Pub. B.V., POB 211, 1000 AE Amsterdam, Netherlands V.1- 1964-
NTPTR* National Toxicology Program Technical Report Series. Research Triangle Park, NC 27709 No.206-

TUMORIGENIC EFFECTS JOURNAL REFERENCES:
BJCAAI British Journal of Cancer. Macmillan Press Ltd., Houndmills, Basingstoke, Hants. RG21 2XS, UK V.1- 1947-
NTPTR* National Toxicology Program Technical Report Series. Research Triangle Park, NC 27709 No.206-

TOXICITY EFFECTS JOURNAL REFERENCES:
AIHAAP American Industrial Hygiene Association Journal. AIHA, 475 Wolf Ledges Pkwy., Akron, OH 44311 V.19- 1958-
ARTODN Archives of Toxicology. Springer-Verlag, Heidelberger Pl. 3, D-1000 Berlin 33, Fed. Rep. Ger. V.32- 1974-
BJIMAG British Journal of Industrial Medicine. British Medical Journal, Box 560B, Kennebunkport, ME 04046 V.1- 1944-
GISAAA Gigiena i Sanitariya. For English translation, see HYSAAV. V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR V.1- 1936-
NTIS** National Technical Information Service. Springfield, VA 22161 Formerly U.S. Clearinghouse for Scientific & Technical Information.
TXAPA9 Toxicology and Applied Pharmacology. Academic Press, Inc., 1 E. First St., Duluth, MN 55802 V.1- 1959-

34ZIAG Toxicology of Drugs and Chemicals, Deichmann, W.B., New York, Academic Press, Inc., 1969

OTHER MULTIPLE DOSE EFFECTS JOURNAL REFERENCES:
NTPTR* National Toxicology Program Technical Report Series. Research Triangle Park, NC 27709 No.206-

REVIEWS JOURNAL REFERENCES:
DTLVS* The Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) booklet issues by American Conference of Governmental Industrial Hygienists ACGIH, Cincinnati, OH, 1996

STANDARDS & REGULATIONS JOURNAL REFERENCES:
CFRGBR Code of Federal Regulations. U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402
DTLVS* The Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) booklet issues by American Conference of Governmental Industrial Hygienists ACGIH, Cincinnati, OH, 1996

NTP, NIOSH, EPA STATUS JOURNAL REFERENCES:
NTPTR* National Toxicology Program Technical Report Series. Research Triangle Park, NC 27709 No.206-

DATA PRESENT: Irritation Effects; Mutation Effects; Tumorigenic Effects; Toxicity Effects; Human Toxicity Effects; Other Multiple Dose Effects; Reviews; Standards and Regulations; NIOSH Criteria Documents; NTP, NIOSH, EPA Status

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$3.69 Estimated cost this search
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Background Document C, Reference 21

Nemeth, G., 1989, *RCRA Facility Assessment Report - Edgewood Area - Aberdeen Proving Ground, Maryland No. 39-26-0490-90*, Waste Disposal Engineering Division, U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, Md., Nov.

See Background Document B, Reference 40

Background Document C, Reference 22

Panel on Cholinesterase Reactivator Chemicals, Panel on Psychochemicals, and Panel on Irritants and Vesicants, 1984, *Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents. Volume 2: Cholinesterase Reactivators, Psychochemicals, and Irritants and Vesicants*, prepared for the Department of the Army, Washington, D.C., by the National Research Council, National Academy Press, Washington, D.C., June.

See Background Document B, Reference 41

LD# 2014

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ERDEC-TR-042

VAPOR PRESSURE DATA ANALYSIS OF DICHLOROFORMOXIME

Elwin C. Penski

RESEARCH AND TECHNOLOGY DIRECTORATE

March 1993

U.S. ARMY
CHEMICAL
AND BIOLOGICAL
DEFENSE AGENCY

Aberdeen Proving Ground, Maryland 21010-5423

Disclaimer

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorizing documents.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE 1993 March	3. REPORT TYPE AND DATES COVERED Final, 92 May - 92 Nov

4. TITLE AND SUBTITLE
Vapor Pressure Data Analysis of Dichloroformoxime

5. FUNDING NUMBERS
PR-10162622A553

6. AUTHOR(S)
Penski, Elwin C.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
DIR, ERDEC,* ATTN: SCBRD-RTC,
APG, MD 21010-5423

8. PERFORMING ORGANIZATION REPORT NUMBER
ERDEC-TR-042

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
*When this work was performed, ERDEC was known as the U.S. Army Chemical Research, Development and Engineering Center, and the author was assigned to the Research Directorate.

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)
Dichloroformoxime is an irritant widely reported in the international literature. For such compounds, it is necessary to have reliable information available on vapor pressures and the properties derived from vapor pressures (saturation vapor concentrations, boiling point, enthalpies of vaporization, etc.). In response to requests that the vapor pressure data for dichloroformoxime be reviewed for consistency, the literature was examined, and the little data found in the literature was combined, fitted, and analyzed to make the best use of the data available. The fit to the Antoine equation is fairly poor. The boiling point is calculated to be 128.5 °C, ± 8.5 °C. The best estimates and 95% confidence expected deviations of the calculated vapor pressures, saturation vapor concentrations, and enthalpies of vaporization are provided over a range of temperatures.

14. SUBJECT TERMS
Volatility
Vapor pressure
Antoine equation
Enthalpy of vaporization
Concentration of saturated vapor

15. NUMBER OF PAGES
19

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
UNCLASSIFIED	UNCLASSIFIED	UNCLASSIFIED	UL

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PREFACE

The work described in this report was authorized under Project No. 10162622A553, CB Defense/General Investigation. This work was started in May 1992 and completed in November 1992.

The use of trade names or manufacturers' names in this report does not constitute an official endorsement of any commercial products. This report may not be cited for purposes of advertisement.

Acknowledgments

Special thanks are due to Corky Smith and Patsy A. D'Eramo, Jr. of the Information Services Division, Management Information Services Division, ERDEC, for their extensive help in locating reports and information. The comments of Parker Ferguson, Helen M. Walker, and Ann Brozena of the Research and Technology Directorate, ERDEC, are also greatly appreciated.

*When this work was performed, ERDEC was known as the U.S. Army Chemical Research, Development and Engineering Center, and the author was assigned to the Research Directorate.

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VAPOR PRESSURE DATA ANALYSIS OF DICHLOROFORMOXIME

1. INTRODUCTION

Dichloroformoxime* is an irritant widely reported in the international literature.[1-8] Vapor pressures are one of the most important liquid properties[9] determining or influencing the volatility, reactivity, persistency, toxicity, flammability, solubility, and transfer processes of chemicals. Thus, it is necessary to have reliable information available on vapor pressures and the properties derived from vapor pressures for such compounds. Saturation vapor concentrations, boiling point, and enthalpies of vaporization are some of the properties derived from vapor pressures.

In response to requests that the vapor pressure data for dichloroformoxime be reviewed for consistency, a literature search was performed and the little data found in the literature was combined, fitted, and analyzed to make the best use of the data available.

2. BACKGROUND

2.1 Theory.

In this report, the data is fitted to the Antoine equation. The Antoine equation,[9] the most widely used equation to fit vapor pressure data, is equation 1.

$$\log_{10} P = A - B/(t + C) \tag{1}$$

where

P	=	vapor pressure in Torr
t	=	temperature in °C
A, B, C	=	constants

*The names for this compound found in the literature are: dichlorformoxim, dichlorformaldoxim, dichloroximinomethan, dichlorformaldehyd-oxim, kohlensaure-dichlorid-oxim, dichlormethylen-hydroxylamin, phosgene oxime, and phosgen-oxim. Its chemical formula is $Cl_2C{=}NOH$, and its registry number is 1794-86-1.

Equation 2 makes it possible to calculate enthalpies of vaporization from the temperature and the Antoine constants.

$$\Delta H_v = \frac{\log_e 10\ RBT^2}{(C+t)^2} \quad (2)$$

where

ΔH_v = enthalpy of vaporization in kilocalorie per mole

T = temperature in Kelvin

R = ideal gas law constant (1.9872 cal K^{-1} mol^{-1})

Since the early 20th century, the term "volatility" has been defined as follows by the military of the world.[9]

$$\text{Volatility} = PM/RT \quad (3)$$

M is the compound molecular weight, and R is 82.053 cm^3 atm K^{-1} mol^{-1}.

Volatility as defined by equation 3 is usually called the *concentration of saturated vapor*. The concentration of saturated vapor is based on the ideal gas law that is fairly accurate at vapor pressures below one atmosphere in pressure. The units of grams or milligrams per cubic meter have been nearly always used. Other definitions of volatility that have been used are given in reference 9 (Appendix C).

2.2 Computations and Plotting.

The program used is named "ANT193.BAS" and is written in MS-DOS GW-BASIC for IBM compatible personal computers. It is a slightly modified version of "ANT592.BAS" that was reported in reference 9. The methods of indexing organic compounds and abbreviating references used in the program are given in reference 9. Plotting is performed with "ProPLOT", which is a 2-D scientific plotting software package sold by Cogent Software (Menlo Park, CA) that creates PostScript printer output. The plotting was done on a Hewlett Packard LaserJet III (Brisbane, CA). The computations were run on a Swan Technologies (State College, PA) 386/33 personal computer.

3. RESULTS

Table 1 contains the literature and calculated vapor pressures for dichloroformoxime, percent difference, experimental method, and reference code at each experimental temperature. The Antoine constants and their standard deviations are given in Table 2.

The correlation coefficient was 0.9958, which appears to be excellent, but the standard statistical F value was 4.35 at the 95% confidence level -- too high. The F value was 2.02 at the 80% confidence level. This indicates only a fair fit. The deviations of the calculated vapor pressures at the 95% confidence level are given in Tables 3 and 4. The boiling point was found to be 128.5 °C, ± 8.5 °C at the 95% confidence level and 128.5 °C, ± 5.8 °C, at the 80% confidence level. The molecular weight was calculated to be 113.93. The computer program estimated that 15 digits are required for the calculation. Figure 1 shows a plot of the logarithm of dichloroformoxime vapor pressures versus $-1/(t+C)$. Figures 2 and 3 provide simple vapor pressure versus temperature plots with error bars.

4. DISCUSSION

The data in this report was extracted from numerous organic synthesis reports where boiling points at various atmospheric pressures are reported. Usually the exact methodology used to obtain the data is not reported. Such data makes up the foundation of vapor pressure found in the literature, handbooks, and data bases. Very little data has been measured for the purpose of obtaining vapor pressure data or heats of vaporization.

If precise values of vapor pressures, saturation vapor concentrations, enthalpies of vaporization, or some other property based on vapor pressures are required, additional measurements must be made.

5. CONCLUSIONS

As a result of this study, the following conclusions are provided:

- The vapor pressure data found in the literature was only a few very imprecise boiling points at various atmospheric pressures.

Table 1. Comparison of Calculated Vapor Pressures with Experimental Data for Dichloroformoxime

Temperature	Vapor Pressure		Difference	Measurement Method	Reference
	Experimental	Calculated			
Celsius	Torr	Torr	Percent		
47.0	1.800D+01	2.066D+01	14.80	Boiling Point	30BIR/SEN
48.0	2.700D+01	2.182D+01	-19.18	Boiling Point	51REE
53.0	2.800D+01	2.853D+01	1.88	Boiling Point	48GRY/DYM
52.0	2.800D+01	2.705D+01	-3.38	Boiling Point	51REE
62.5	4.000D+01	4.650D+01	16.24	Boiling Point	41EHM/WAL
67.5	5.000D+01	5.952D+01	19.05	Boiling Point	74BOG/BRO
74.0	1.040D+02	8.125D+01	-21.88	Boiling Point	65MAR/KRU
128.0	7.600D+02	7.470D+02	-1.71	Boiling Point	30BIR/SEN
128.8	7.600D+02	7.687D+02	1.14	Boiling Point	29PRA/SEN
129.0	7.600D+02	7.742D+02	1.87	Boiling Point	41MOH

Table 2. Antoine Constants and Their Standard Deviations at the 95% Confidence Level

Constant	Numeric Value	Standard Deviation
A	9.5243146	0.25520
B	2838.40258	92.502
C	298.763	0.0013*

*This is not a standard deviation. Since C was optimized to this interval in the fitting process, a standard deviation would not be meaningful.

■ The best estimates and 95% confidence expected deviations of the calculated vapor pressures, saturation vapor concentrations, and enthalpies of vaporization for dichloroformoxime are provided over a range of temperatures in Tables 3 and 4.

■ The calculated boiling point of dichloroformoxime was found to be 128.5 °C, ± 8.5 °C.

Table 3 . Calculated Values and Error Limits for Dichloroformoxime from 0 to 150 °C

Temperature	Vapor Pressure		Concentration of Saturated Vapor		Heat of Vaporization	
Celsius	Torr	% Error	mg/(m cubed)	% Error	cal/mol	% Error
0.0*	1.06D+00	+/- 55	7.07E+03	+/- 55	10856.	+/-11.8
10.0*	2.15D+00	+/- 47	1.38E+04	+/- 47	10922.	+/-11.8
20.0*	4.17D+00	+/- 40	2.60E+04	+/- 40	10984.	+/-11.8
30.0*	7.78D+00	+/- 34	4.69E+04	+/- 34	11043.	+/-11.8
The melting point is 39 °C. The above are for supercooled liquid.						
40.0*	1.40D+01	+/- 28	8.16E+04	+/- 28	11098.	+/-11.8
50.0	2.43D+01	+/- 23	1.37E+05	+/- 23	11150.	+/-11.8
60.0	4.10D+01	+/- 19	2.25E+05	+/- 19	11199.	+/-11.8
70.0	6.72D+01	+/- 18	3.58E+05	+/- 18	11246.	+/-11.8
80.0	1.07D+02	+/- 17	5.55E+05	+/- 17	11291.	+/-11.8
90.0	1.67D+02	+/- 19	8.41E+05	+/- 19	11333.	+/-11.8
100.0	2.55D+02	+/- 21	1.25E+06	+/- 21	11373.	+/-11.8
110.0	3.81D+02	+/- 24	1.81E+06	+/- 24	11411.	+/-11.8
120.0	5.58D+02	+/- 27	2.59E+06	+/- 27	11448.	+/-11.8
130.0*	8.02D+02	+/- 31	3.64E+06	+/- 31	11482.	+/-11.8
140.0*	1.14D+03	+/- 34	5.02E+05	+/- 34	11516.	+/-11.8
150.0*	1.58D+03	+/- 38	6.83E+06	+/- 38	11547.	+/-11.8

* Extrapolated beyond data range.

Table 4 . Calculated Values and Error Limits for Dichloroformoxime from 20 to 50 °C

Temperature	Vapor Pressure		Concentration of Saturated Vapor		Heat of Vaporization	
Celsius	Torr	% Error	mg/(m cubed)	% Error	cal/mol	% Error
20.0*	4.17D+00	+/- 40	2.60E+04	+/- 40	10984.	+/-11.8
21.0*	4.44D+00	+/- 39	2.76E+04	+/- 39	10990.	+/-11.8
22.0*	4.74D+00	+/- 39	2.93E+04	+/- 39	10996.	+/-11.8
23.0*	5.05D+00	+/- 38	3.11E+04	+/- 38	11002.	+/-11.8
24.0*	5.37D+00	+/- 37	3.30E+04	+/- 37	11008.	+/-11.8
25.0*	5.72D+00	+/- 37	3.51E+04	+/- 37	11014.	+/-11.8
26.0*	6.09D+00	+/- 36	3.72E+04	+/- 36	11020.	+/-11.8
27.0*	6.47D+00	+/- 35	3.94E+04	+/- 35	11026.	+/-11.8
28.0*	6.88D+00	+/- 35	4.18E+04	+/- 35	11031.	+/-11.8
29.0*	7.32D+00	+/- 34	4.42E+04	+/- 34	11037.	+/-11.8
30.0*	7.78D+00	+/- 34	4.69E+04	+/- 34	11043.	+/-11.8
31.0*	8.26D+00	+/- 33	4.36E+04	+/- 33	11048.	+/-11.8
32.0*	8.77D+00	+/- 32	5.25E+04	+/- 32	11054.	+/-11.8
33.0*	9.31D+00	+/- 32	5.55E+04	+/- 32	11060.	+/-11.8
34.0*	9.87D+00	+/- 31	5.87E+04	+/- 31	11065.	+/-11.8
35.0*	1.05D+01	+/- 31	6.21E+04	+/- 31	11071.	+/-11.8
36.0*	1.11D+01	+/- 30	6.56E+04	+/- 30	11076.	+/-11.8
37.0*	1.18D+01	+/- 29	6.93E+04	+/- 29	11082.	+/-11.8
38.0*	1.25D+01	+/- 29	7.32E+04	+/- 29	11087.	+/-11.8
The melting point is 39 °C. The above are for supercooled liquid.						
39.0*	1.32D+01	+/- 28	7.73E+04	+/- 28	11093.	+/-11.8
40.0*	1.40D+01	+/- 28	8.16E+04	+/- 28	11098.	+/-11.8
41.0*	1.48D+01	+/- 27	8.61E+04	+/- 27	11103.	+/-11.8
42.0*	1.57D+01	+/- 27	9.08E+04	+/- 27	11109.	+/-11.8
43.0*	1.66D+01	+/- 26	9.57E+04	+/- 26	11114.	+/-11.8
44.0*	1.75D+01	+/- 26	1.01E+05	+/- 26	11119.	+/-11.8
45.0*	1.85D+01	+/- 25	1.06E+05	+/- 25	11124.	+/-11.8
46.0*	1.96D+01	+/- 25	1.12E+05	+/- 25	11130.	+/-11.8
47.0	2.07D+01	+/- 24	1.18E+05	+/- 24	11135.	+/-11.8
48.0	2.18D+01	+/- 24	1.24E+05	+/- 24	11140.	+/-11.8
49.0	2.30D+01	+/- 23	1.31E+05	+/- 23	11145.	+/-11.8
50.0	2.43D+01	+/- 23	1.37E+05	+/- 23	11150.	+/-11.8

* Extrapolated beyond data range.

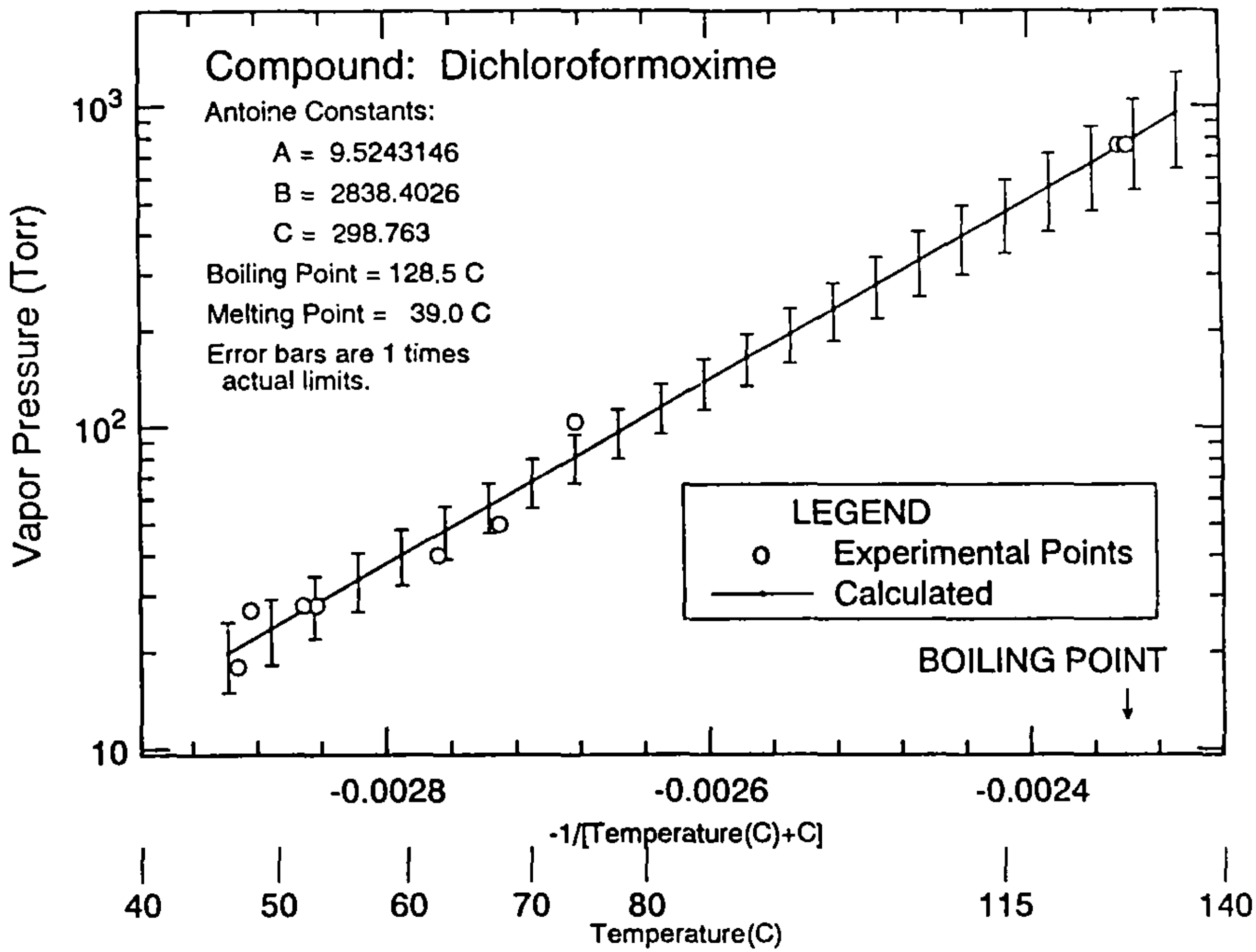

Figure 1. Logarithm of Vapor Pressures Versus -1/(t+C)

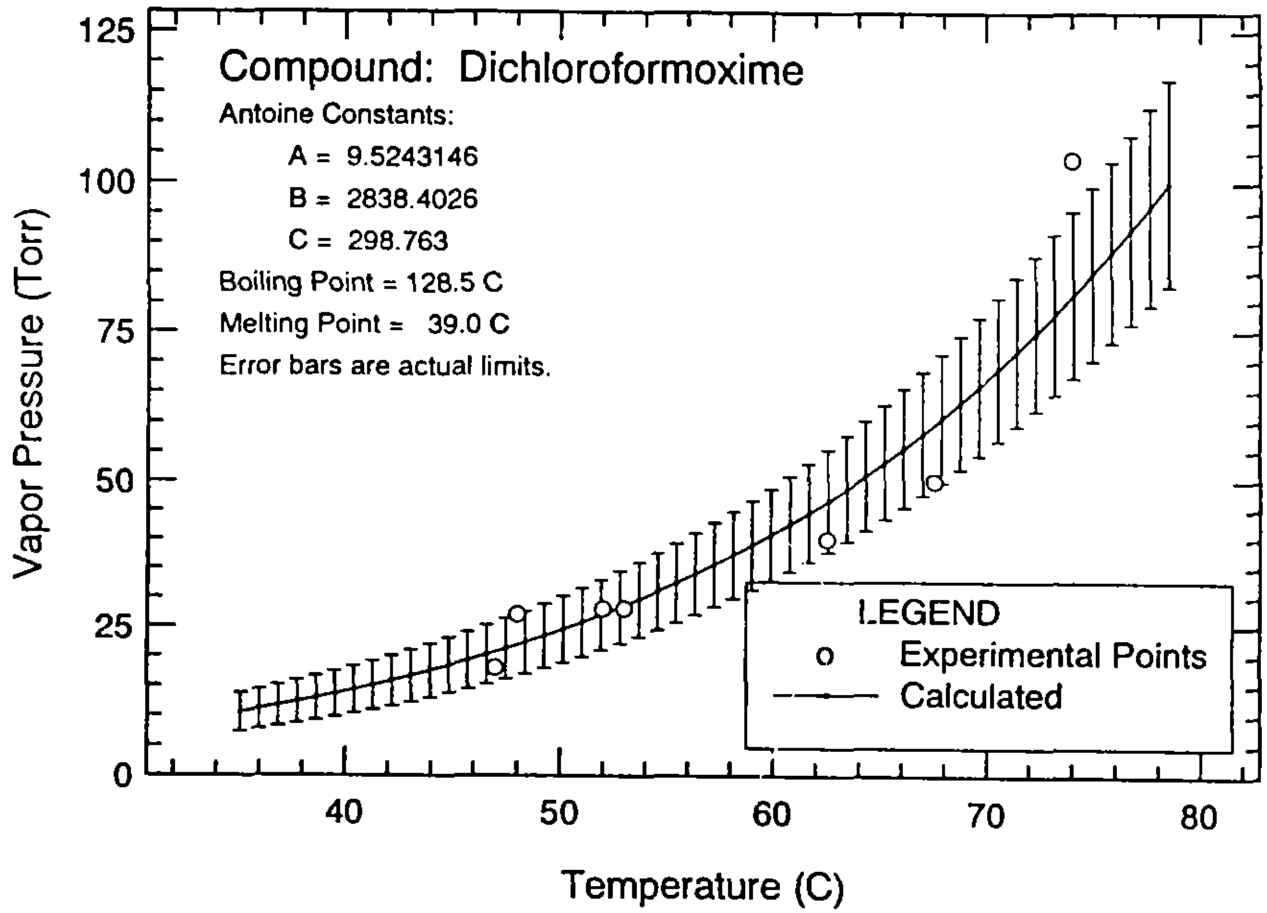

Figure 2. Vapor Pressures Versus Temperature Plot, 30 to 80 °C

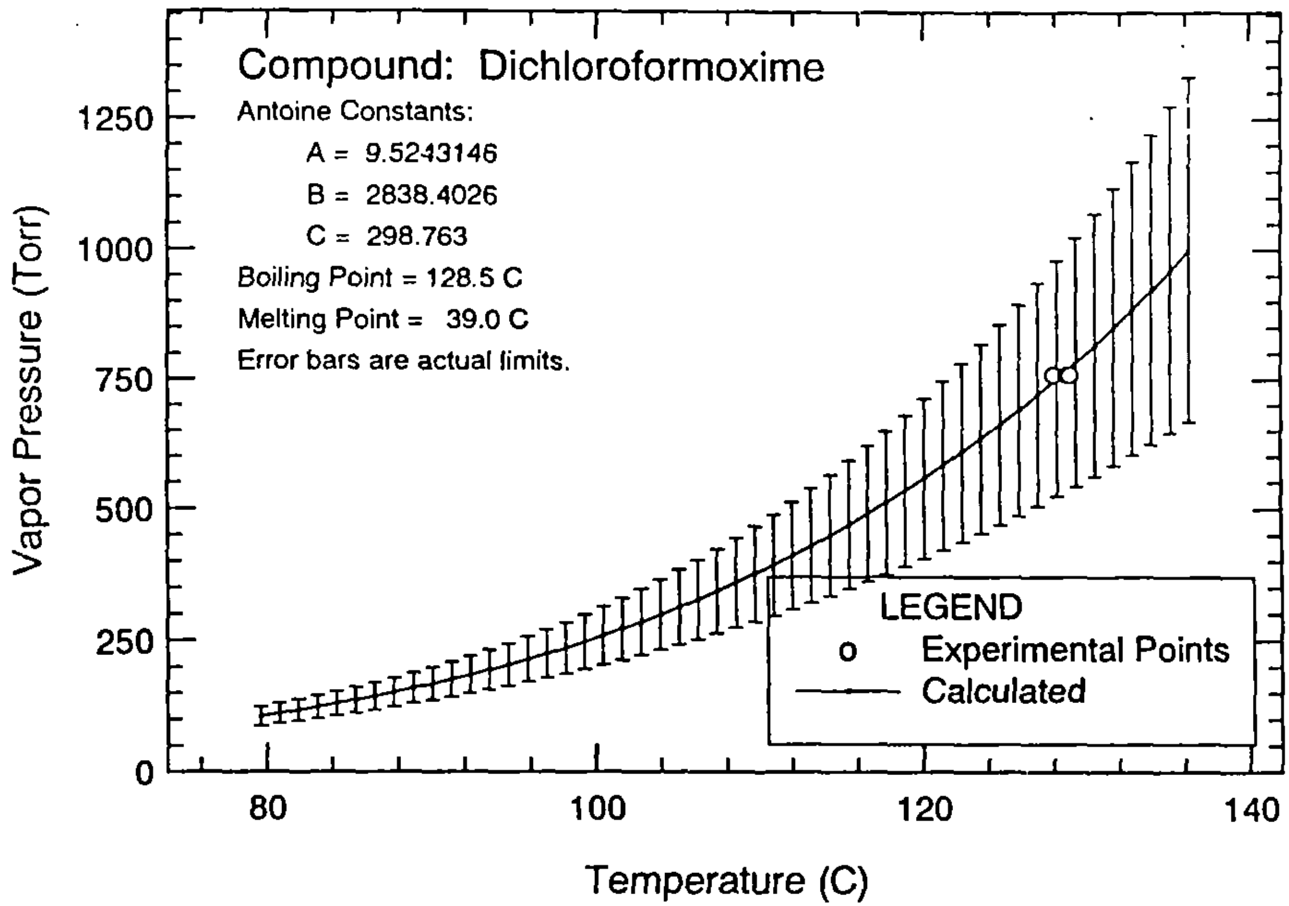

Figure 3. Vapor Pressures Versus Temperature Plot, 75 to 140 °C

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9. Penski, E.C., Vapor Pressure Data Analysis Methodology, Statistics, and Applications, CRDEC-TR-386, U.S. Army Chemical Research Development and Engineering Center, Aberdeen Proving Ground, MD, July 1992, UNCLASSIFIED Report (AD A255090).

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APPENDIX

LITERATURE CITED KEYED TO REFERENCE CODE*

29PRA/SEN Prandtl, W., and Sennewald, K., "Trichloronitrosomethane, Dichloroformoxime and Their Derivatives," Chemische Berichte Vol. 62, p 1766 (1929).

30BIR/SEN Birckenbach, L., and Sennewald, K., "Pseudo-Halogens, XV. The Reaction of Fulminic Acid and its Salts with Halogens," Justus Liebigs Annalen der Chemie Vol. 482, p 19 (1930).

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41EHM/WAL Ehman, P.J., and Walker, W.O., U.S. Patent 2,299,742, October 27, 1941.

41MOH Mohler, H., "Synthesis and Properties of Irritants", Protar Vol. 7, No. 4, (1941).

48GRY/DYM Gryszkiewicz-Trochimowski, E., Dymowski, K., and Schmidt, E., "A Novel Method for Preparing Dichloroformoxime," Societe Chemique de France: Bulletin, No. 5, p 597 (1948).

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CHEMICALS IN WAR

A Treatise on Chemical Warfare

BY
AUGUSTIN M. PRENTISS, Ph.D.
Lieutenant Colonel, Chemical Warfare Service
United States Army

WITH CHAPTERS ON THE
Protection of Civil Populations
and International Situation

BY
GEORGE J. B. FISHER
Major, Chemical Warfare Service, United States Army

First Edition

McGRAW-HILL BOOK COMPANY, Inc.
NEW YORK AND LONDON
1937

Introduction

Agent	Introduced by	Date
Simple lacrimators		
Ethylbromacetate	French	August, 1914
Xylyl bromide	Germans	January, 1915
Benzyl bromide	Germans	March, 1915
Brommethylethyl ketone	Germans	July, 1915
Ethyliodoacetate	British	September, 1915
Benzyl iodide	French	November, 1915
Brombenzyl cyanide	*French*	~~July, 1918~~
Chloracetophenone	Americans	Postwar
Toxic lacrimators		
Chloracetone	French	November, 1914
Bromacetone	Germans	July, 1915
Iodoacetone	French	August, 1915
Acrolein	French	January, 1916
Chlorpicrin*	Russians	August, 1916
Phenylcarbylamine chloride*	Germans	May, 1917

* Primarily lung injurants.

GROUP CHARACTERISTICS

The lacrimators, as a group, have certain well-defined properties in common, the most important of which are the following:

1. They all have the power to irritate certain tissues only, *i.e.*, the eyes, and without producing noticeable lesions; their action is thus both elective and reversible since they affect only one organ, and the irritation produced quickly disappears.

2. Their threshold of action is low, *i.e.*, they are effective in extremely low concentrations, such as a few thousandths of a milligram per liter, and can produce an intolerable atmosphere in concentrations as low as one-thousandth of that required for the most effective lethal agents.

3. They are quick acting, producing almost instantaneous physiological effects (in less than 1 minute) in the form of a muscular reaction of the eyelids, closing the eyes, and a glandular reaction from the lacrimatory glands, producing a copious flow of tears.

4. Chemically they are very closely related, being formed by a central atom of carbon, carrying a halogen and one or several negative groups in which the hydrogen atoms are readily displaced. Hederer and Istin (15), quoting Professor Job, give the following type formulas which explain the chemical relationships of the lacrimators to each other:

$$H_2{=}C \begin{cases} -\left\{\begin{array}{l} \text{Cl (chloride)} \\ \text{Br (bromide)} \\ \text{I (iodide)} \end{array}\right. \\ \diagdown C_6H_5 \text{ (benzyl)} \end{cases}$$

CHEMICALS I

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WORLD WAR LUNG INJURANTS

The principal lung-injurant agents in order of their chronological appearance in the World War, are:

Agent	Introduced by	Date
Simple lung injurants		
Chlorine	Germans	April 22, 1915
Methylsulfuryl chloride	Germans	June, 1915
Ethylsulfuryl chloride	French	June, 1915
Monochlormethylchloroformate	Germans	June 18, 1915
Dimethyl sulfate	Germans	August, 1915
Perchlormethylmercaptan	French	September, 1915
Phosgene	Germans	Dec. 19, 1915
Trichlormethylchloroformate	Germans	May 19, 1916
Chlorpicrin	Russians	August, 1916
Phenylcarbylamine chloride	Germans	May, 1917
Dichlordimethyl ether	Germans	January, 1918
Dibromidimethyl ether	Germans	
Toxic lung injurants		
Phenyldichlorarsine	Germans	September, 1917
Ethyldichlorarsine	Germans	March, 1918
Phenyldibromarsine	Germans	September, 1918

Chlorine (Cl_2)

French: "Bertholite"

Chlorine was the first gas used on an effective scale in war. It was employed by the Germans against British and French Colonial troops at Ypres, Belgium, on Apr. 22, 1915, when 168 tons of chlorine were released from 5,730 cylinders on the front of 6 kilometers. It was effective to a distance of 5 kilometers downwind and caused 15,000 casualties, of which 5,000 were fatal.

During the war chlorine was the principal gas used for cloud-gas attacks. At first, when the Allies had little or no means of protection, it was a very effective weapon and caused many thousands of casualties. Later in the war, when troops were protected with masks, the effectiveness of chlorine was greatly reduced. However, in mixtures with other gases, such as phosgene and chlorpicrin, it continued to be used throughout the war.

At ordinary temperatures and pressures, chlorine is a greenish yellow volatile gas with a pungent odor and caustic poisonous characteristics.

:ll; if sufficient hydrochloric acid is
shell. Because of its rapid hydroly-
ıe cannot be efficiently employed in

rhich is considerably below ordinary
.poration is so slow that it has to be
rine in order to set up satisfactory
l. This was the manner in which
attacks throughout the war.
en times that of chlorine, a concen-
tal after 10 minutes' exposure. In
n met in battle, one or two breaths

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is products—hydrochloric acid and
ie upper air passages of the body,
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ufficient phosgene is decomposed in
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ges, so that men exposed to this gas
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ı and men gassed with it often have
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christ (24, pages 7 to 9) says:

ation of the trachea or bronchi; coughing
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e to carry on his work for an hour or two
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ass into collapse. There are records of
attack and who seem to have suffered
later upon attempting physical effort.
This edema is at first noncellular but,
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s are seldom found in the exudate; later
is time reveals focal patches of broncho-
is the outstanding condition. After the

second or third day, if death does not occur, the edema fluid is resorbed and recovery follows, barring complication of the bronchopneumonic process.

The important immediate effects of phosgene are practically limited to the lungs. These changes consist of damage to the capillaries. This damage may be noted a half hour after gassing. The capillaries in the walls of the alveoli are markedly constricted and appear collapsed. Later they become dilated and engorged with blood, and blood stasis is the rule. Frequently thrombi form and block the capillaries for some distance, which increases the blood stasis. This dilation and blood stasis in the capillaries is the main cause of pulmonary edema; the latter progresses rapidly from this time on.

A number of theories have been advanced to explain the production of edema. The preponderance of evidence as to the cause of the edema following phosgene gassing is that it is due to local injury of the endothelial cells which results in an increased capillary permeability; the other changes in the blood and in the circulation are secondary to the trauma sustained by the capillary wall.

The injurious effects of phosgene are materially increased by physical exertion. Frequently those parts of the lungs which have not been damaged by the gas would be sufficient for breathing purposes if the body were at rest, but they are not sufficient while the body is in motion, particularly in view of the excess carbonic acid which is formed in the body by the decomposition of the phosgene.

Phosgene is manufactured in industry by the original process of direct synthesis of chlorine and carbon monoxide, as indicated in Chart X. The only change from the original process of making it is the substitution of a catalyst (animal charcoal) for the action of sunlight.

Compared to chlorine, phosgene has the following advantages as a chemical agent. It is:

1. Far more toxic (0.50 mg. per liter at 10 minutes).
2. A little less volatile and more persistent.
3. Greater vapor density (3.5).
4. More insidious in action.
5. Chemically more inert and, therefore, more difficult to neutralize and protect against.

The principal disadvantages of phosgene are its slower physiological action on the body and its inability to discharge itself from cylinders at a sufficient rate for cloud-gas attacks.

In addition to the foregoing, phosgene is relatively easy to protect against and for that reason would probably be displaced in the future by gases of greater toxicity and more difficult to neutralize.

Trichlormethylchloroformate ($ClCOOCCL_3$)

German: "Perstoff"; French: "Surpalite"; British: "Diphosgene"

This gas was first used in the World War by the Germans at Verdun in May, 1916, in retaliation for the French phosgene shell which were introduced in February, 1916.

Trichloromethylchloroformate is the completely chlorinated methyl ester of formic acid and is obtained by completing the chlorination of the monochlormethylchloroformate (K-Stoff). In studying the chlorinated methyl esters of formic acid, the German chemists found that their toxic properties increased, while their lacrimatory powers decreased, with

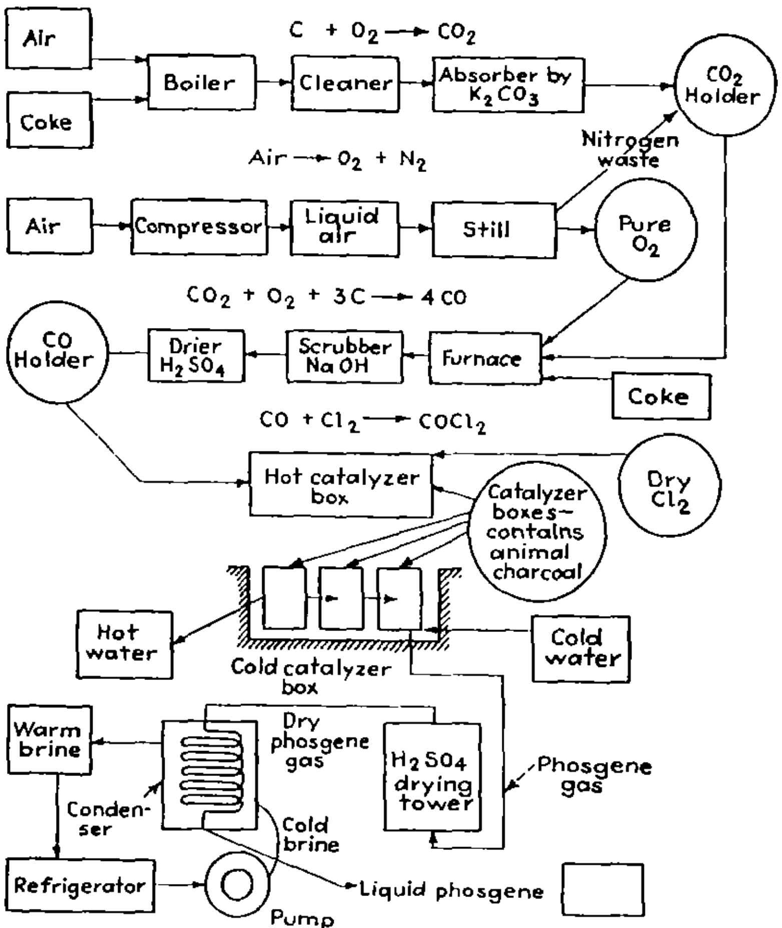

CHART X.—Catalytic manufacture of phosgene (flow sheet).

the addition of chlorine atoms in the methyl group of their molecular structures. Thus, diphosgene, which contains the maximum chlorine atoms, was found to be the least lacrimatory but the most toxic of these compounds and was for that reason substituted for K-Stoff as the standard German nonpersistent lethal gas for shells. An analysis of the gas casualties of the late war indicates that, on the basis of the total

number of fatalities, diphosgene was the principal *killing* gas used *in shells* during the war.

Trichlormethylchloroformate is an oily liquid of specific gravity 1.65 and a disagreeable suffocating odor. It boils at 127°C. (260.6°F.), giving off a dense whitish vapor 6.9 times heavier than air, which persists on open ground about 30 minutes. At 20°C. (68°F.), its volatility is 26.00 mg. per liter. When heated to about 350°C. (662°F.) or upon contact with moisture, as in the tissues of the body, trichlormethylchloroformate breaks down, yielding two molecules of phosgene, thus: $ClCOOCCl_3 = 2COCl_2$, from which it received its English name—diphosgene. Under ordinary conditions of temperature and pressure, it hydrolyzes slowly, ultimately yielding carbonic acid and hydrochloric acid, according to the following equation:

$$ClCOOCCl_3 + 2H_2O = 2CO_2 + 4HCl$$

Because of its high boiling point and the fact that in its primary form it is relatively inactive physiologically, diphosgene is peculiarly adapted for shell filling. Unlike phosgene, which requires artificial refrigeration to keep it below its boiling point during filling operations, diphosgene can be filled into shells in the field, the workmen requiring no other protection than gas masks. This was of great advantage to the Germans during the war as it enabled them to fill shell close behind the front lines, and the filled shell thus required the minimum transportation, handling, and storage. Because of this fact, the Germans were able to use all sorts of H.E. shell for gas by the simple expedient of cementing the joints in the shells, while the Allies, whose shell were filled far from the front and had to withstand much rough handling and long storage, could not successfully use cemented gas shell, because of leakage difficulties.

The toxicity of diphosgene is about the same as that of phosgene. In fact, it is probable that the toxicity of diphosgene is not a specific property of that compound, but is derived from the phosgene molecules into which it decomposes in the tissues of the body.

The German chemist, Haber (1), quoting the work of Flury, gives the toxicity index of diphosgene as 500, as compared to 450 for phosgene. For a 10-minute exposure, this is equivalent to a concentration of 0.050 mg. per liter of diphosgene and 0.045 mg. per liter of phosgene. American determinations, however, show that the minimum lethal concentrations of phosgene for a 10-minute exposure is 0.50 mg. per liter which is over ten times the German figure. Many reasons have been advanced to account for the large discrepancy in these figures, such as that Flury's determinations were on cats which were subsequently found to be peculiarly sensitive to phosgene and diphosgene concentrations. The cats were also said to be undernourished, which still further increased

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Phenyldichlorarsine ($C_6H_5AsCl_2$)

German: "Blue Cross No. 1"; French: "Sternite"

This compound is primarily a toxic lung injurant and is therefore treated in Chap. VII, page 165. In addition to its lung-injurant effect, however, it also exerts a considerable respiratory-irritant action, and for that reason, was used by the Germans in "Blue Cross 1" shell in mixture with, and as a solvent for, diphenylcyanarsine.

As phenyldichlorarsine was not used alone during the war, there is no war data available as to its effectiveness by itself. When mixed with diphenylchlorarsine or diphenylcyanarsine, in approximately equal proportions, as it was used in the war, the mixture appears to have a more irritating and toxic effect than either of the latter compounds when used alone. The 50–50 mixture produces toxic smokes similar in character to those produced by pure diphenylchlorarsine, but somewhat denser and slightly less penetrating as regards the gas mask.

Because of its high toxicity and not inconsiderable vesicant effect, in addition to its respiratory-irritant action, phenyldichlorarsine is to be ranked among the most valuable of the World War gases.

Ethyldichlorarsine ($C_2H_5AsCl_2$)

German: "Dick"

This compound is also primarily a toxic lung injurant and has been treated as such in Chap. VII. It is also a rather powerful respiratory irritant. A concentration as low as 0.0038 mg. per liter (1:1,900,000) produces a slight irritation of the throat; 0.0125 mg. per liter (1:570,000) strongly irritates the nose and throat and produces a burning sensation in the chest which persists for about an hour after exposure ceases.

Ethyldichlorarsine was introduced by the Germans in an attempt to produce a quick-acting nonpersistent vesicant and was first called "Yellow Cross 1." It was soon found, however, that it was not very effective as a vesicant, but proved to be highly toxic and its classification was changed to "Green Cross 3." It was thereafter used primarily as a lung-injurant agent.

Its combined toxic, irritant, and vesicant effects, together with its low persistency and quick action make it a valuable war gas for offensive use.

Ethyldibromarsine

This compound is the bromine analogue of ethyldichlorarsine and its properties are almost identical therewith. It was used in the war only as a mixture with ethyldichlorarsine in "Green Cross 3" shell and data

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Background Document C, Reference 25

Roberts, W.C., and W.R. Hartley, 1992, *Drinking Water Health Advisory: Munitions*, Lewis Publishers, Boca Raton, Fla.

See Background Document B, Reference 46

Rosenblatt & Burrows in

Supplement F

The chemistry of **amino, nitroso and nitro compounds and their derivatives** Part 2

Edited by
SAUL PATAI
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1807 175 YEARS OF PUBLISHING 1982

JOHN WILEY & SONS
CHICHESTER – NEW YORK – BRISBANE – TORONTO – SINGAPORE
An Interscience ® Publication
1982

CHAPTER **25**

Oxidation of amines

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As may be readily imagined, various characteristics of amine oxidations are repeated or modified to a degree in oxidations with other oxidants, especially those that operate in one-electron steps. A review by Chow and coworkers[55], which focused on the intermediate nonaromatic aminium radicals, served to compare a number of these and to integrate a corpus of relevant information. In a different sort of comparison with the effects of other oxidants, a few one-electron amine oxidations in aqueous solution, including chlorine dioxide reactions, were correlated by means of the following equations with the ionization potentials (IP) or Taft σ^* values of the amines and the redox potentials of the oxidants[154]:

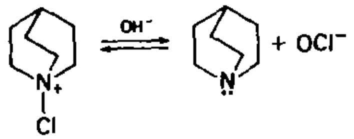
$$\log k_1 = -7.84\, E^0 - 5.31\, IP + 3.85 \tag{16}$$

or

$$\log k_1 = -7.64\, E^0 - 4.78 \Sigma\sigma^* - 3.47 \tag{17}$$

III. HALOGENATING AGENTS

The halogenating agents of major interest are chlorine, bromine and iodine (to a far lesser degree), the corresponding hypohalous acids and a variety of *N*-halogenated amines and amides. In most cases, these agents transfer positive halogen to unshared amine electrons, with formation of *N*-haloammonium ions from tertiary amines and haloamines from primary or secondary amines. The tertiary amine-derived *N*-chloroammonium ions are usually unstable; thus, although Ellis and Soper[91] observed that dry trimethylchloroammonium chloride, formed in carbon tetrachloride, is stable for several days, the triethyl analogue could not be prepared. Both *N*-chloroammonium ions form in aqueous solution; these ions decompose oxidatively, as described later, but also react with chloride ion in a partial reversal of the chlorination reaction[91]. *N*-Chloroquinuclidinium ion (**4**) is exceptional; it can be hydrolysed to quinuclidine but does not undergo oxidative decomposition[144] (equation 18).



(18)

(**4**)

Crane and coworkers[62] reported that amines containing the β-chloroethyl group underwent both α- and β-chlorination in carbon tetrachloride, the latter reaction slightly predominating; hydrolysis of the resultant products produced aldehydes and secondary amines. This has been the only report in recent years to suggest that chlorine is introduced directly to the α- or β-carbons of aliphatic amines, but it is also one of the few concerned with chlorination in nonpolar media. Detailed examination of the oxidative dealkylation of tertiary amines in acidic aqueous hypochlorous acid solution suggested the sequence shown in reactions (19)–(23)[294]. The 'product' **7** remained undefined because reaction (20) could be interpreted as either abstraction of an α-proton from **6** by **5** (reaction 24) to give **8**, or electrophilic attack by **6** on the α-carbon of **5** to yield **9** (reaction 25). Both **8** and **9** (i.e. versions of **7**) would hydrolyse to R_2NH and R^1CHO. Although reaction (24)

$$\underset{(\mathbf{5})}{R_2(R^1CH_2)N\!:} + HOCl \longrightarrow \underset{(\mathbf{6})}{R_2(R^1CH_2)\overset{+}{N}\text{—}Cl} \tag{19}$$

$$R_2(R^1CH_2)\overset{+}{N}\text{—}Cl + \mathbf{5} \longrightarrow \mathbf{5} + \underset{(\mathbf{7})}{\text{'product'}} \tag{20}$$

$$\mathbf{7} \xrightarrow[H_2O]{} R_2NH + R^1CHO \tag{21}$$

$$R_2NH + HOCl \longrightarrow R_2NCl \tag{22}$$

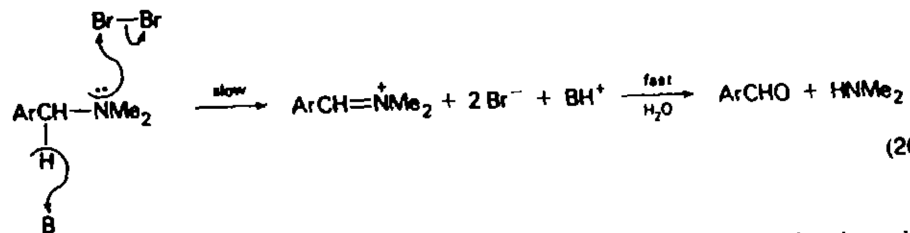
$$R_2NH + R_2(R^1CH_2)\overset{+}{N}\text{—}Cl \longrightarrow R_2NCl + R_2(R^1CH_2)NH^+ \tag{23}$$

$$\mathbf{6} + \mathbf{5} \longrightarrow R_2\overset{+}{N}(Cl)\text{—}\overset{H}{\underset{\cdot\cdot}{C}}\text{—}R^1 \longrightarrow \underset{(\mathbf{8})}{R_2\overset{+}{N}\text{=}CH_2} + Cl^- \tag{24}$$

$$\mathbf{6} + \mathbf{5} \longrightarrow \underset{(\mathbf{9})}{R_2N\text{—}\overset{H}{\underset{Cl}{C}}\text{—}R^1} + H^+ \tag{25}$$

is more attractive than (25), Taraszka[294] excluded it. He reasoned that if the tertiary amine played the role of a general base catalyst, acetate ion should also be a general base catalyst here; yet it is not.

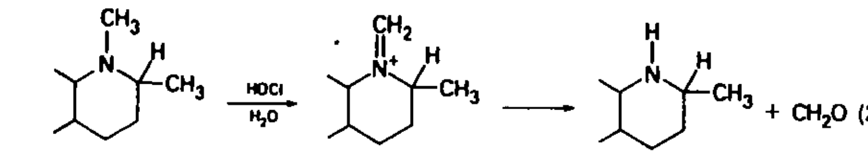
Differences from the foregoing are seen with Br_2. Lee and Srinivasan[183], in studies on dimethylbenzylamines, confirmed speculation by Deno and Fruit[87] to the effect that Br_2 attacks the nitrogen electron pair in concert with general base attack on an α-hydrogen (reaction 26). Both Br_2[183] and HOCl[263] show preferred benzyl



(26)

cleavage of dimethylbenzylamines, whereas ClO_2 cleavage is proportional to the number of α-hydrogens[263]. Moreover, Br_2 attack favours ring oxidation of *N*-methylpyrrolidine and *N*-methylpiperidine, in contrast to a greater tendency towards *N*-methyl oxidations by HOCl[87] and ClO_2[118], thus, Deno and Fruit[87] concluded that the Br_2 reaction is not promising for *N*-demethylation of alkaloids, unlike HOCl. The pronounced selectivity for ring oxidation over demethylation by Br_2 was demonstrated by studies on the alkaloids nicotine[88] and conanine[243,244]. Even with HOCl, less methyl cleavage (though still significant) than ring oxidation was seen with conanine[244]. The studies by Picot and Luschini on reactions of alkaline Br_2 and I_2 and sodium hypochlorite with conanine and related alkaloids provide examples of the diversity of possible reactions[244]. When a methyl proton is eliminated, loss of formaldehyde quickly ensues (reaction 27). However, with elimination of a ring proton, complex products can result, e.g. reaction (28).

N-Haloamides oxidize tertiary amines in a manner very similar to that of hypo-



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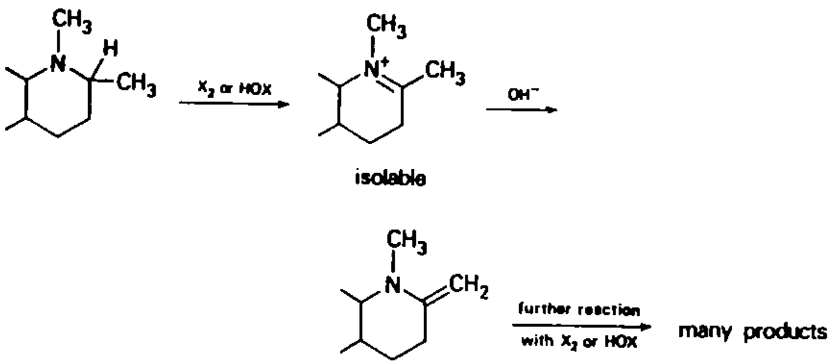
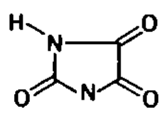


(28)

halous acids. Inasmuch as these reactions are usually carried out in nonaqueous media, vinylamine-type products (enamines) are often the result[89,151].

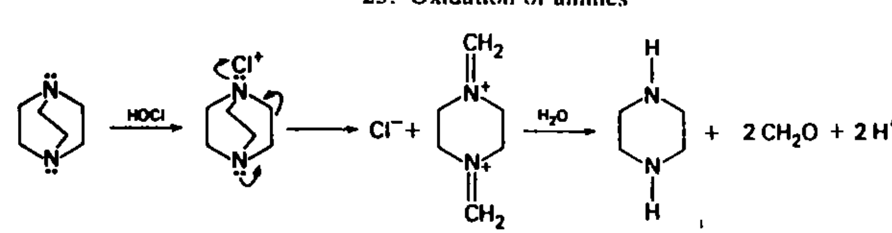
Purine and pyrimidine bases also undergo sequential halogenation reactions. Initially, *N*- and *C*-halogenated intermediates are formed, which are often quite stable[83,84a,153,240,295]. However, when the reaction mixtures stand for a long time, especially in the continued presence of excess active halogen species, more extensive reactions take place, accompanied by ring disruption. For example, nitrogen trichloride, carbon dioxide and trichloroacetic acid are produced by HOCl from uracil at pH 7[85] and chloroform at higher pH[217]; acetic acid, trichloracetic acid and isobutyramidinium ion, along with a little chloroform, result from HOCl attack on 2-isopropyl-4-methyl-6-pyrimidinol[83,84a]. Guanine, adenine and xanthine slowly form parabanic acid (**10**), whereas caffeine and theophylline produce *N,N'*-dimethylparabanic acid when treated with the same reagent[153].



(**10**)

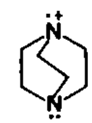
A number of other nitrogenous water supply constituents yield chloroform on treatment for several hours with hypochlorous acid/hypochlorite ion at neutral pH, indicating extensive oxidation; chloroform yields increase as the pH is raised to 11[217]. Notable among these water supply constituents are hydroxyproline, tryptophane, indole, *m*-aminophenol and chlorophyll. Several other compounds produce chloroform only at elevated pH, with maximum yields at pH 8.5–10.5. Chlorine consumption also indicates that other oxidations occur, though they do not lead to chloroform[217].

In addition to such oxidative dealkylations or ring oxidations as were shown previously, 1,2-diamines can undergo oxidative fragmentation. An outstanding example is reaction (29)[259]. The intermediate, **11**, also appears to undergo reversible homolysis, as discussed later. Perchloryl fluoride is another oxidant capable of

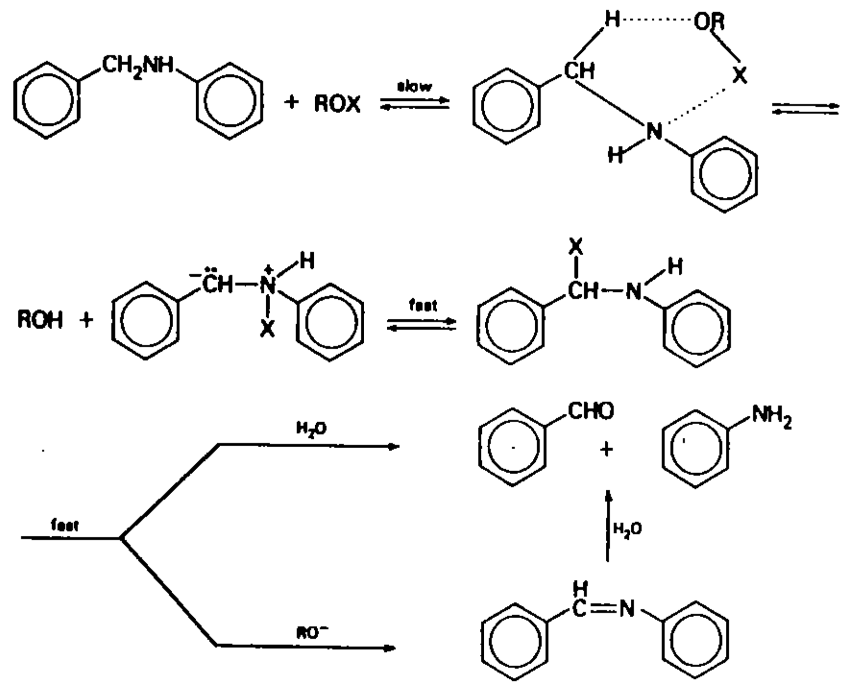


(**3**) (**11**) (**12**) (29)

converting **3** to **12**[111]. Consensus seems to favour two-electron pathways in these oxidations[40,87,183,294]; in particular, evidence for this is the fact that light has no effect on the bromination reaction[87,183]. Nevertheless, homolytic cleavage of the N—Cl bond may give rise to the free radicals in the reaction mixtures, as demonstrated by the ability of a mixture of HOCl and triethylamine to initiate acrylonitrile polymerization[150] and by the easily observed formation of the red aminium radical intermediate **13** when triethylenediamine reacts with HOCl[259,261]. Moreover, one-electron transfer to give aminium ion intermediates was implicated in the amine-catalysed bromination of olefins by *N*-bromosuccinimide[74] and in amine oxidations by 1-chlorobenzotriazole[205].



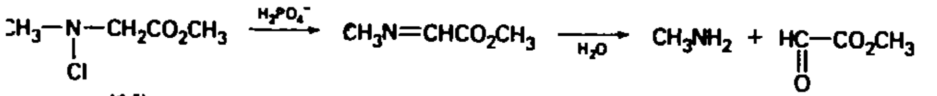
(**13**)



(30)

Product and kinetic studies by Ogata and Nagura[229] on the secondary amine *N*-benzylaniline demonstrated that hypohalite attack in methanol cannot involve an *N-halogenated intermediate; when solutions of such intermediates are made* alkaline, aniline ring substitution (halogen or methoxy) invariably results. Based on product isolation and on kinetics with only iodine-containing solutions (because chlorine and bromine are rapidly consumed in organic solvents), they proposed the mechanism shown in reaction (30).

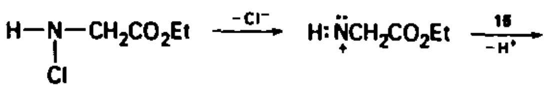
At pH 7, HCl elimination from **14** is general base-catalysed[164] (reaction 31).



(31)

(14)

A slight change from structure **14** gives a compound **15**, whose decomposition is unaffected by general base[164]. The nitrenium ion pathway suggested by Kaminski and coworkers[164] (equation 32) borrows from the nitrene mechanism proposed by Pinchuk and coworkers[245] (equations 33 and 34).



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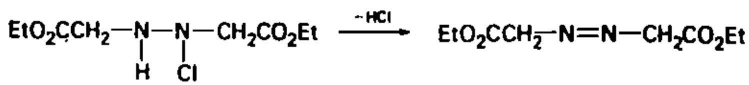
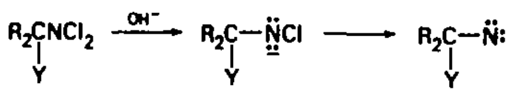
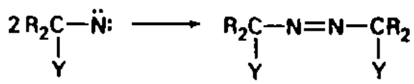


(32)



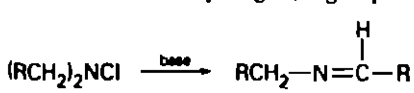
(33)

Y = CN, PO(OEt)$_2$ or CO$_2$Me



(34)

These equations, (33) and (34), do not exclude the numerous examples wherein *N*-chlorinated secondary or primary amines undergo conversion to imines (and thence by hydrolysis to carbonyl compounds[13,45,90,134,175,198,267]. Here, the initial step *could well be attack of base on an α-hydrogen, e.g. equations* (35)–(37).



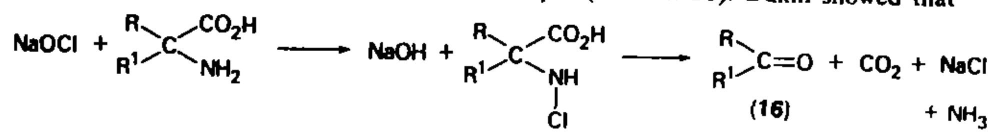
(35)

$$RCH_2NHCl \xrightarrow{\text{base}} RCH{=}NH \qquad (36)$$

$$RCH_2NCl_2 \xrightarrow{\text{base}} RCH{=}NCl \xrightarrow{\text{base}} RCN \qquad (37)$$

Although a number of mono- and di-chloroamines and bromoamines have been prepared, pure or in aqueous solution, they are not very stable; this seems to be especially true of the bromoamines[175,216]. Excess bromine in pH 6 buffer converted dipropylamine to a mixture of pyruvic and propionic acids; propylamine gave propionic acid as the sole product, even with equimolar Br$_2$[87].

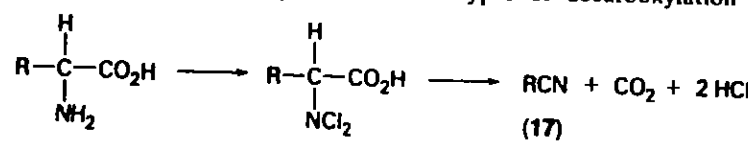
In the literature of amine halogenation, the reactions of amino acids and peptides occupy a special place. As early as 1909, Langheld[181] reported the oxidative decarboxylation of α-amino acids at neutral pH (reaction 38). Dakin showed that



(16)

(38)

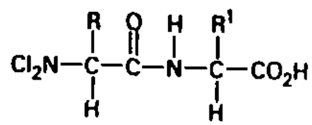
chlorosulphonamides could also act as the chlorinating agents[70], and later that two moles of sodium hypochlorite[70], or chlorosulphonamide[71] produced nitriles (reaction 39). Hypobromite oxidations gave the same types of decarboxylation products



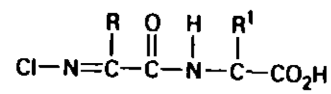
(17)

(39)

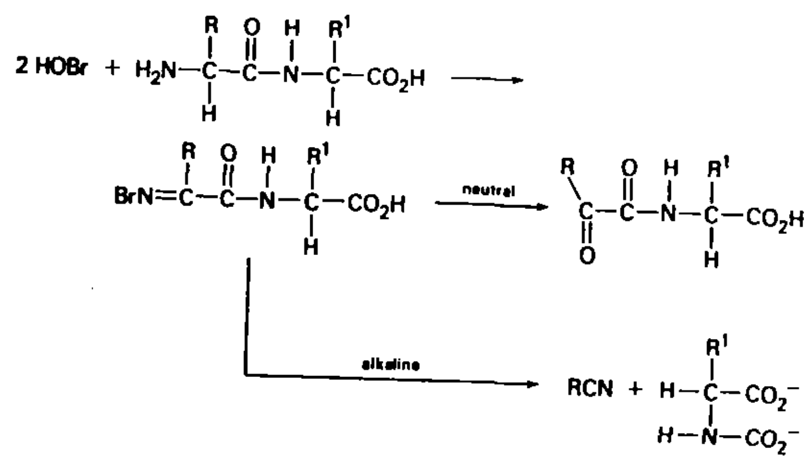
(**16** or **17**)[106,117]. *N,N*-Dichloropeptides (**18**), which decomposed on standing to *N*-chloroimides (**19**), were isolated on treatment of dipeptides with hypochlorous acid[242]. Goldschmidt and coworkers[117] elaborated on the bromination of dipeptides as shown in reaction (40).



(18)

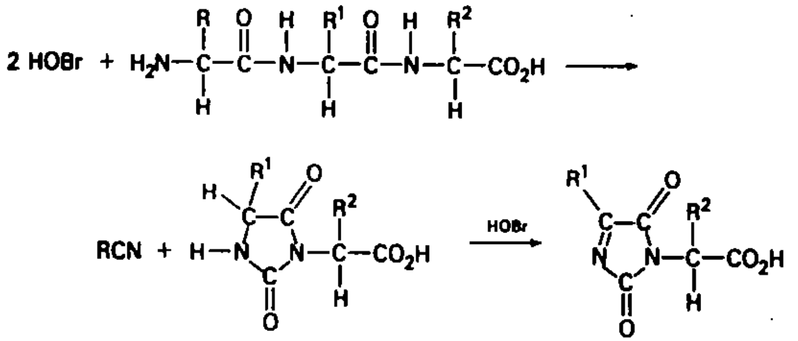


(19)



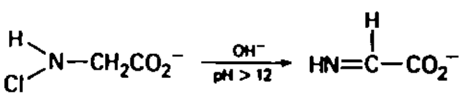
(40)

They found carbamino acid (**20**) to be moderately stable in alkaline solution; the amino group was thus protected from further attack by hypobromite. Loss of the *N*-carboxy function as carbon dioxide occurred quickly on acidification. With tripeptides, a hydantoin and then a dehydrohydantoin were obtained[115,116] (reaction 41).



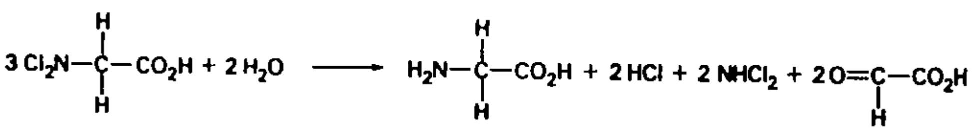
(41)

Glycine and certain of its peptides show some atypical chemistry, which cannot be fully presented here. It is most important to remember, however, that the product of type **17**, in the case of glycine, is HCN, which undergoes further reaction with hypohalites to form the cyanogen halide[66] or cyanate ion[117]. Culver[66] concluded that *N*-chloroglycine forms iminoacetate in strongly alkaline solution (equation 42); it rapidly disproportionates in acidic solution to glycine and *N,N*-dichloroglycine. The latter appears by a first-order process in the pH range 5.1–8.5

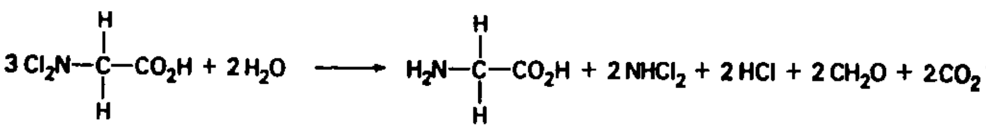


(42)

to form HCN and CO_2 as discussed earlier. Culver[66] was less certain about the mode of decomposition of *N,N*-dichloroglycine, but slightly favoured reaction (43) over (44). In a very similar reaction, van Tamelen and coworkers[297] reported that



(43)

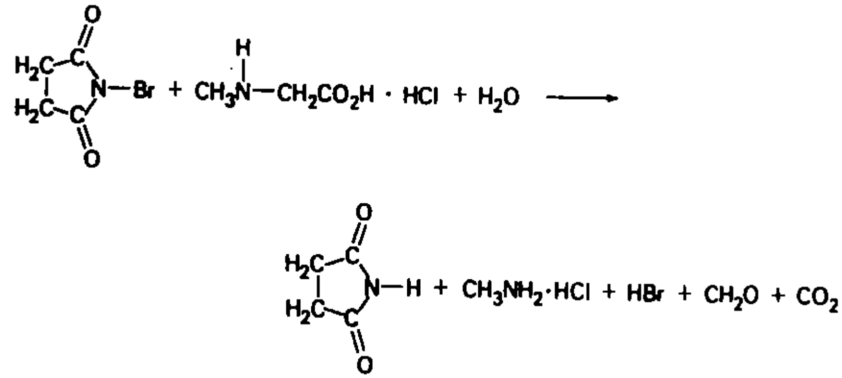


(44)

oxidation of *N,N*-dimethylglycine with one mole of hypochlorous acid in the pH range 1.5–6.3 showed maximum decarboxylation at pH 1.5 (reaction 45).

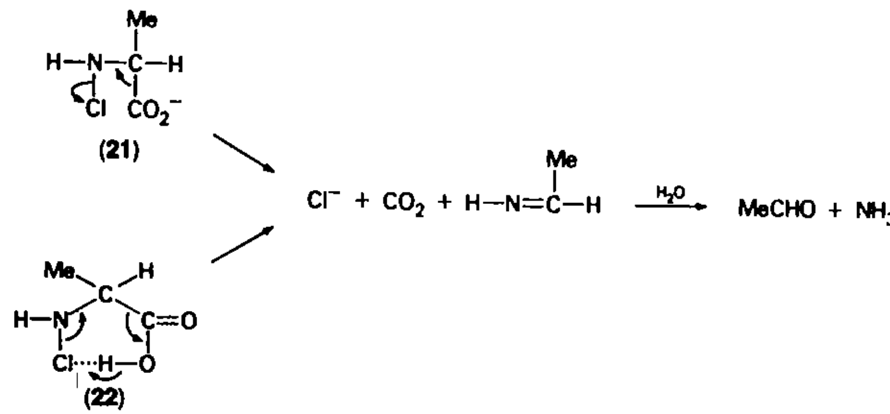
$$Me_2N{-}CH_2CO_2H + HOCl \longrightarrow Me_2NH + CH_2O + CO_2 + HCl \qquad (45)$$

N-Methylglycine, when treated with *N*-bromosuccinimide under acidic conditions, also yielded formaldehyde[271] (reaction 46). The decomposition rate of *N*-chloro-*N*-methylglycine was shown to be independent of buffer concentration at pH 7[164].

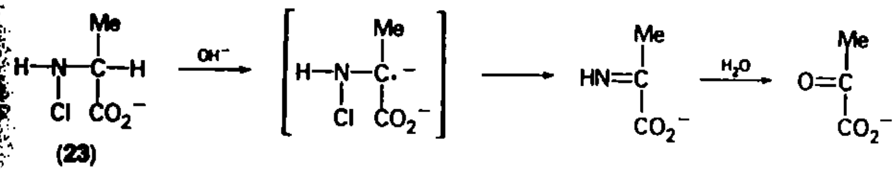


(46)

Among recent studies on the mechanism of such amino acid oxidations, that of Stanbro and Smith[286] is noteworthy for its integration of the kinetics of *N*-chloroalanine decomposition with product identification to formulate a picture of the variation of reaction pathways with pH. They indicated the existence of two decarboxylative pathways, the second of which was earlier suggested by Fox and Bullock[105] (reaction 47). Although Fox and Bullock[105] explained the higher pH formation of pyruvic acid by a carbanion intermediate (equation 48), Stanbro and

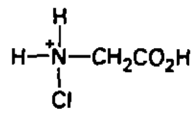


(47)



(48)

Smith[286] found that the kinetics did not justify such a mechanism. The scheme of Stanbro and Smith[286] also required kinetic terms for the autodecomposition and acid-catalysed decomposition of the most protonated species (**24**), though they wrote no mechanism and did not specify the products (probably those of oxidative



(24)

decarboxylation). They completely described the kinetics at 25°C over the pH range 1.5–7.5 by an equation involving species **21**, **22** and **24**.

The importance of halogen transfer to, from and among amino nitrogens is apparent in the foregoing discussion. Rates and equilibria of chlorine transfer have been determined by a number of investigators, most notably Soper and Smith[284], Weil and Morris[303,304], Culver[66], Friend[107], Higuchi and coworkers[144], Kaminski and coworkers[165], Higuchi and Hasegawa[143], Pitman and coworkers[246], Hussain and coworkers[158], Gray[119], Gray and coworkers[120] and Margerum and coworkers[210]. Particularly significant has been the development of values and correlations for chlorine potential, $-\log_{10}K_{cp}$, where:

$$K_{cp} = \frac{[R_2NH][HOCl]}{[R_2NCl]} \text{ or } \frac{[R_3N][HOCl]}{[R_3NCl^+]} \tag{49}$$

Although chlorine transfer could occur via hydrolysis to HOCl, Hussain and coworkers[158] and Margerum and collaborators[210] showed conclusively that direct nitrogen-to-nitrogen transfer occurs much more rapidly.

Hypobromous acid appears to halogenate amines about 3–5 times faster than hypochlorous acid[216], but the evidence so far is fragmentary.

IV. POTASSIUM FERRICYANIDE

Lindsay Smith's group[6,7,8,203,204] has produced the most important mechanistic studies of the ferricyanide oxidation of tertiary alkylamines. The concentration of ferricyanide ion is easy to follow spectrophotometrically at the 420 nm absorption maximum. Unlike many other complexed metal ions, neither the oxidized (ferricyanide) nor the reduced (ferrocyanide) form readily loses its ligands. Ferricyanide is not a particularly reactive oxidant (compared, for example, to chlorine dioxide). For this reason, most of the oxidation experiments have been conducted at high pH, where enough of the amine free base can be present to react with reasonable speed. To dissolve the required concentrations of amines, it has usually been necessary to employ mixed organic–aqueous solvents, such as *t*-butylamine–water or methanol–water[55].

The ferricyanide oxidation mechanisms (equations 50–53) parallel corresponding chlorine dioxide mechanisms in many details (see equation 2). One notable

$$RCH_2\ddot{N}R^1_2 + Fe(CN)_6^{-3} \longrightarrow RCH_2\overset{+\cdot}{N}R^1_2 + Fe(CN)_6^{-4} \tag{50}$$

$$RCH_2\overset{+\cdot}{N}R^1_2 \longrightarrow R\dot{C}H{-}\ddot{N}R^1_2 + H^+ \tag{51}$$

$$R\dot{C}H{-}\ddot{N}R^1_2 + Fe(CN)_6^{-3} \longrightarrow RCH{=}\overset{+}{N}R^1_2 + Fe(CN)_6^{-4} \tag{52}$$

$$RCH{=}\overset{+}{N}R^1_2 + H_2O \longrightarrow \left[\begin{array}{c} RCH{-}NR^1_2 \\ | \\ OH \end{array}\right] \longrightarrow RCHO + R^1_2NH \tag{53}$$

Background Document C, Reference 27

Rosenblatt, D.H., et al. (editors), 1975, *Problem Definition Studies on Potential Environmental Pollutants; II: Physical, Chemical, Toxicological, and Biological Properties of 16 Substances*, Technical Report 7509, U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, Md.

See Background Document B, Reference 48

Background Document C, Reference 28

Rosenblatt, D.H., et al., 1996, *Background Chemistry for Chemical Warfare Agents and Decontamination Processes in Support of Delisting Waste Streams at the U.S. Army Dugway Proving Ground, Utah*, ANL/EAD/TM-56, Argonne National Laboratory, Argonne, Ill., April.

See Background Document B, Reference 50

THE WAR GASES

CHEMISTRY AND ANALYSIS

BY

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With 20 Figures and 14 Tables

1943.

NEW YORK

D. VAN NOSTRAND COMPANY, INC.

250 FOURTH AVENUE

These compounds all have lachrymatory power, especially tetrachloro dinitro ethane, which is much more powerful in this respect than chloropicrin.

Some of the halogenated derivatives of unsaturated nitro-compounds have also been examined, *e.g.*, *chloronitro ethylene* ($CH_2 = CClNO_2$) and various of its homologues.[1] These compounds, though having powerful lachrymatory properties, cannot be considered for use as war gases for owing to the presence of the unsaturated linkage in their molecules they tend to polymerise forming substances without lachrymatory properties.

Recently other substances having a certain amount of interest in war gas chemistry have been prepared:

(1) *Trifluoronitroso methane*,[2] obtained by the action of fluorine on silver cyanide in the presence of silver nitrate, is a bright blue gas, fairly stable chemically. It melts at $-150°$ C., boils at $-80°$ C. and has an unpleasant odour.

(2) *Trichloronitroso methane*,[3] obtained by the action of nitric acid on the sodium salt of trichloromethyl sulphinic acid, is a liquid boiling at 5° C. at 70 mm. pressure.

Both these substances have an irritant action.

PS

1. Trichloro Nitroso Methane. CCl_3NO (M.Wt. 148)

Trichloronitroso methane has been prepared recently by Prandtl and Sennewald[4] by the action of nitric acid on the sodium salt of trichloromethyl sulphinic acid:

$$SO_2\left\langle\begin{matrix}CCl_3\\H\end{matrix}\right. + HNO_3 = CCl_3NO + H_2SO_4$$

A very violent reaction takes place and the yield of trichloro nitroso methane is low. This compound is more conveniently obtained by the action of an aqueous solution of sodium trichloro methyl sulphinate, potassium nitrate and sodium nitrite on sulphuric acid.[5]

LABORATORY PREPARATION

250 ml. 20% sulphuric acid are placed in a round-bottomed flask fitted with a tap-funnel and a well-cooled coil-condenser. The flask is heated to 70° C. and a cold solution of 94 gm. sodium trichloromethyl sulphinate, 50 gm. potassium nitrate and 25 gm. sodium nitrate in 300 ml. water is dropped in from the tap-funnel,

[1] WILKENDORF, *Ber.*, 1924, **57**, 308; SCHMIDT and RUTZ, *Ber.*, 1928, **61**, 2142.
[2] O. RUFF, *Ber.*, 1936, **69**, 598, 684.
[3] PRANDTL and SENNEWALD, *Ber.*, 1929, **62**, 1754.
[4] PRANDTL and SENNEWALD, *loc. cit.*

regulating the rate of addition so that the internal temperature is maintained at 70° C. by the heat of reaction. The contents of the flask suddenly turn blue and the trichloronitroso methane commences to distil, collecting in the receiver, which is cooled by ice, as a blue liquid. The yield is 75–80%.

PHYSICAL AND CHEMICAL PROPERTIES

It is a dark blue liquid which when boiled at ordinary pressures partially decomposes. It boils undecomposed at 5° C. at a pressure of 70 mm. Its specific gravity is 1·5 at 20° C.

It is insoluble in water, but dissolves in the common organic solvents. On storing at ordinary temperature in a sealed glass container, it decomposes in 2–3 months with formation of nitrosyl chloride, oxides of nitrogen and chloropicrin. It is much more stable in solution.

It reacts slowly with aqueous alkaline solutions and rapidly in presence of ether.

Oxygen and oxidising agents transform it into various compounds, among which chloropicrin has been identified. On reduction with hydrogen sulphide, dichloro formoxime (see p. 77) is formed:

$$CCl_3NO + H_2S \rightarrow Cl_2 = C = NOH + S + HCl.$$

The vapour of trichloronitroso methane strongly attacks rubber.

Both in the liquid and the vapour states it has a disagreeable odour; irritation is caused to the eyes and to the respiratory tract, lachrymation and coughing being produced.

2. Chloropicrin. CCl_3NO_2 (M.Wt. 164·5)

Chloropicrin, or trichloronitromethane, was prepared in 1848 by Stenhouse.[1] In the war of 1914–18 it was largely employed as a war gas, more particularly as it combined a simple and economic manufacture with many of the characteristic desiderata of a war gas.

It was first employed by the Russians in 1916 in hand-grenades, dissolved in sulphuryl chloride (50%).

Chloropicrin is also known as "*Klop*" (Germany), "*Aquinite*" (France), and "*PS*" (America).

It has found application as an insecticide and fungicide[2] and has been used for eradicating rats from ships.[3]

[1] STENHOUSE, *Ann.*, 1848, **66**, 241.
[2] [illegible]

Preparation

Various methods have been proposed for the preparation of chloropicrin. For example:

(1) By the action of picric acid on calcium hypochlorite.[1]

(2) By the action of chlorine on nitromethane or mercury fulminate.[2]

(3) By the action of nitric acid on certain chlorinated organic compounds, as chloroform,[3] chloral,[4] trichloroethylene,[5] etc.

(4) By the action of a mixture of nitric and hydrochloric acids on the by-products of acetone manufacture.[6]

The method which was most used during the war of 1914–18 was that of the action of picric acid on calcium hypochlorite. This method was not very suitable in practice, for it required as raw material a substance not easily spared during the war, when it was needed for the explosive industry. The other methods of production referred to above have been studied since the war, showing the interest of chemists in working out a method which does not require the use of a raw material of limited accessibility.

Laboratory Preparation

Chloropicrin may be prepared in the laboratory by the method proposed by Hoffmann.[7]

550 gm. chloride of lime made into a paste with about 1 litre water are placed in a 5-litre flask. A paste of sodium picrate, made by mixing 50 gm. picric acid with 10 gm. sodium hydroxide and 250 ml. water, is added with continuous stirring. The flask is then fitted with a stopper carrying a long condenser and the contents steam-distilled until no more oily droplets come over.

The reaction takes place very rapidly and is completed in about ½ hour. The oily distillate is separated from the water in a separatory funnel, dried over calcium chloride and redistilled.

Yield 70% of the theoretical.

Industrial Manufacture

The various methods used during the war for the manufacture of chloropicrin do not differ greatly from Hoffmann's method given above.

[1] Stenhouse, *Ann.*, 1848, **66**, 241; Hoffmann, *Ann.*, 1866, **139**, 111.
[2] Kekulé, *Ann.*, 1857, **101**, 204.
[3] Mills, *Ann.*, 1871, **160**, 117.
[4] Kekulé, *Ann.*, 1857, **101**, 212; N. Danaila and Soare, *Bul. chim. soc. românǎ ştiinte*, 1932, **35**, 53.
[5] R. Burrows and Hunter, *J. Chem. Soc.*, **1932**, 1357.
[6] G. Sanna, *Rend. sem. fac. sci. Cagliari*, 1933, **2**, 87.
[7] Hoffmann, *Ann.*, 1866, **139**, 111.

In the German plants a paste of chloride of lime and water was treated in large vessels of 2–3 m. diameter and 4–5 m. depth with picric acid added in small amounts at a time, the temperature being maintained at about 30° C. The mixture was then distilled in a current of steam, the distillate being collected in large receivers where the chloropicrin was separated from water.

The Americans preferred to use calcium picrate instead of the sparingly soluble picric acid, proceeding in the following manner[1]:

A paste of chloride of lime was first prepared and pumped into a vertical vessel of enamelled iron where it was mixed with calcium picrate prepared previously by mixing picric acid with water and an excess of lime. The mixture was allowed to react at ordinary temperatures for about 2 hours and then a current of steam was introduced at the bottom of the vessel. In these conditions the rise in temperature accelerated the reaction and at 85° C. the chloropicrin began to distil. Distillation was continued until no more chloropicrin came over.

According to a patent by Orton and Pope,[2] chloropicrin may also be obtained by the direct action of chlorine on picric acid, or other nitro-derivative of phenol or of naphthol:

$$C_6H_2(NO_2)_3OH + 11Cl_2 + 5H_2O = 3CCl_3NO_2 + 13HCl + 3CO_2.$$

The reaction is carried out in alkaline solution (sodium or potassium hydroxide, or a mixture of the corresponding carbonates) so as to dissolve the nitro-compound and to neutralise the hydrochloric acid which otherwise impedes the chlorination of the picric acid. The reaction takes place very readily at a low temperature (between 0 and 5° C.).

Recently a new method of preparation of chloropicrin has been worked out in Rumania.[3] This uses petroleum as raw material. The principal stages of the preparation of chloropicrin by this process are as follows:

(*a*) Nitration of hydrocarbons present in the petroleum.

(*b*) Chlorination of the nitro-compounds obtained with chloride of lime.

(*c*) Distillation of the chloropicrin in a current of steam.

Physical and Chemical Properties

Chloropicrin in the pure state is a slightly oily, colourless, refractive liquid with a characteristic odour. The crude product is yellow due to impurities.

[1] Trumbull and coll., *J. Ind. Eng. Chem.*, 1920, **12**, 1068.
[2] Orton and Pope, *Brit. Pat.*, 142,878/1918.
[3] Radulescu and Secareanu, *Antigaz*, 1927, No. 6, 3.

It boils at 112° C. at 760 mm. pressure and at 49° C. at 40 mm. of mercury.[1] It solidifies at − 69·2° C.

It may be distilled in a current of steam without decomposition.

The specific gravity of chloropicrin between 0° and 50° C. is as follows:

TEMPERATURE (° C.)	S.G.	TEMPERATURE (° C.)	S.G.
0	1·6930	30	1·6400
10	1·6755	40	1·6219
20	1·6579	50	1·6037

The coefficient of expansion at various temperatures is as follows:

At 0° C.	0·00102	At 30° C.	0·00106
At 10° C.	0·00103	At 50° C.	0·00110

Its specific heat between 15° and 35° C. is 0·235; its latent heat of evaporation is 59 calories. Its vapour density compared with that of air is 5·69. The vapour tension of chloropicrin at any temperature t may be calculated empirically [2] by employing the formula (see p. 5):

$$\log p = 8{\cdot}2424 - \frac{2045{\cdot}2}{273 + t}$$

In the following table the values of the vapour tension are reported together with the corresponding volatilities at various temperatures [3]:

TEMPERATURE ° C.	VAPOUR TENSION MM. HG.	VOLATILITY MGM./CU.M.
0	5·91	57,120
10	10·87	101,400
15	14·12	129,400
20	18·91	170,300
25	23·81	210,900
30	30·50	265,700
35	40·14	343,800
50	80·7	659,300

[1] Cossa, *Gazz. chim. Ital.*, 1872, **2**, 181.
[2] Baxter and Bezzenberger, *J. Am. Chem. Soc.*, 1920, **42**, 1386.

The solubility of chloropicrin in water is very low; according to Thompson and Black [1] 100 gm. water dissolve the following amounts of chloropicrin:

° C.	GM.
0	0·22
10	0·19
20	0·17
30	0·15
40	0·14
75	0·11

The solubility of water in chloropicrin is also very low:

° C.	GM. IN 100 GM. WATER
32	0·1003
36	0·1185
48	0·1647
55	0·2265

These low mutual solubilities facilitate their separation in the preparation and render drying of the chloropicrin unnecessary, unless it is to be employed for some special purpose, as, for example, in "*NC*" mixture (80% chloropicrin and 20% stannic chloride).

Chloropicrin dissolves easily in benzine, carbon disulphide and ethyl alcohol (1 part dissolves 3·7 parts chloropicrin at water-bath temperature). In ether it is, however, relatively sparingly soluble. (At 11° C., 5 volumes ether dissolve 1·5 volumes chloropicrin—Cossa.)

Chloropicrin is a fairly stable compound. It is not hydrolysed by water [2] and not attacked by mineral acids like hydrochloric, nitric and sulphuric, either cold or hot. Only 20% oleum decomposes it with formation of phosgene and nitrosyl sulphuric acid.[3]

On heating to 112° C., according to some authorities (Stenhouse, Cossa, etc.), it distils unchanged, while, according to others,[4] when maintained gently boiling it partially decomposes into phosgene and nitrosyl chloride:

$$CCl_3NO_2 \rightarrow COCl_2 + NOCl.$$

The presence of some metals like copper, tin, zinc, aluminium, iron and lead only slightly influences the velocity of decomposition even at boiling point.[5]

[1] T. Thompson and Black, *J. Ind. Eng. Chem.*, 1920, **12**, 1066.
[2] P. Rona, *Z. ges. expt. med.*, [illegible], **13**, 16.
[3] Secareanu, *Bull.* [illegible]

By passing chloropicrin in the vapour state through a red-hot tube of quartz or porcelain, it decomposes with formation of chlorine and nitric oxide, while hexachloroethane deposits on the cold part of the tube.[1]

According to the researches of Piutti,[2] chloropicrin decomposes as follows when exposed to ultra-violet rays:

$$CCl_3NO_2 \rightarrow NOCl + COCl_2 \rightarrow CO + Cl_2.$$

A similar decomposition takes place when an aqueous solution of chloropicrin is shaken with wood-charcoal, previously activated by treatment with sodium hydroxide and heating to 450° C.[3]

Reducing agents convert it into various products according to the nature of the reducant and the conditions of reduction. Thus Raschig[4] obtained cyanogen chloride with stannous chloride and hydrochloric acid; Geisse,[5] with iron filings and acetic acid, obtained methylamine:

$$CCl_3NO_2 + 6H_2 = CH_3NH_2 + 3HCl + 2H_2O.$$

Frankland[6] observed that the best results are obtained in this reaction by adding the chloropicrin in small portions to a mixture of iron filings and acidified water.

On treatment of chloropicrin with an aqueous solution of sodium or potassium hydroxide there is no reaction, but if alcoholic soda or potash is employed, a gradual decomposition takes place and after a time crystals of potassium chloride separate.

Aqueous ammonia does not react with chloropicrin. However, if the latter is saturated with ammonia gas, or even brought into reaction with an alcoholic solution of ammonia, ammonium chloride and nitrate are formed (Stenhouse). According to Hoffmann,[7] on heating chloropicrin in an autoclave to 100°C. with an alcoholic solution of ammonia, guanidine is formed according to the following equation:

$$CCl_3NO_2 + 3\,NH_3 \rightarrow NH{:}C\left\langle\begin{matrix}NH_2\\NH_2\end{matrix}\right. + 3\,HCl + HNO_3$$

By the action of alcoholic sodium sulphide[8] on chloropicrin also dissolved in alcohol, a violent reaction takes place, heat is

[1] Stenhouse, *Ann.*, 1848, 66, 241.
[2] A. Piutti and Mazza, *Atti accad. sci. Napoli*, 1926, 32, 97.
[3] Alexejevsky, *J. Obscei Khim.*, Ser. A., 1932, 2, 341.
[4] Raschig, *Ber.*, 1885, 18, 3326.
[5] Geisse, *Ann.*, 1859, 109, 284.
[6] Frankland, *J. Chem. Soc.*, 1919, 115, 159.
[7] Hoffmann, *Ber.*, 1868, 1, 145
[8] Krytov and Melnikov, *J. Obscei Khim.*, Ser. A., 1932, 2, 202.

developed and a tarry material separates. According to the conditions of the reaction there are formed carbon monoxide, nitric oxide, nitrogen, carbon dioxide, sodium chloride, sulphur, etc.

$$2\,CCl_3NO_2 + 3\,Na_2S = 3\,S + N_2 + 2\,CO_2 + 6\,NaCl$$

$$2\,CCl_3NO_2 + 3\,Na_2S = 3\,S + 2\,CO + 2\,NO + 6\,NaCl$$

Chloropicrin reacts with sodium or potassium sulphite, forming the corresponding salt of nitromethane disulphonic acid[1]:

$$CCl_3NO_2 + 3Na_2SO_3 + H_2O = CHNO_2(SO_3Na)_2 + 3NaCl + NaHSO_4$$

This reaction must be brought about by heating to 90° to 100° C., and takes place very rapidly in alcoholic as well as aqueous solution. The product of the reaction, sodium nitro methane disulphonate, forms small spheroidal plates, soluble with difficulty in cold water but easily in hot water. According to Rathke,[2] if the reactants are heated excessively a salt is obtained which no longer contains the NO_2-- group and to which he attributes the formula $CH(SO_3Na)_3$.

By the action of potassium bromide on chloropicrin, tribromo nitromethane or bromopicrin is obtained, together with carbon tetrabromide, nitromethane, etc.

Potassium iodide reacts with chloropicrin, giving no triiodo nitromethane, but completely decomposing the molecule with formation of carbon tetraiodide, as follows[3]:

$$CCl_3NO_2 + 4KI = CI_4 + 3KCl + KNO_2.$$

Even in the presence of insufficient potassium iodide, no triiodo nitromethane is formed.

Sodium cyanide in aqueous-alcoholic solution reacts energetically with chloropicrin to form various compounds: sodium chloride, nitrite, carbonate and oxalate, cyanogen chloride, etc.[4]

Chloropicrin reacts even at ordinary temperature with sodium ethylate, forming sodium nitrite and chloride and the tetra ethyl ester of orthocarbonic acid[5]:

$$CCl_3NO_2 + 4C_2H_5ONa = C(OC_2H_5)_4 + 3NaCl + NaNO_2.$$

Sodium methylate reacts similarly.[6] This reaction also takes place when sodium reacts with an alcoholic solution of chloropicrin.[7]

[1] Rathke, *Ann.*, 1872, 161, 153; Backer, *Rec. trav. chim.*, 1930, 49, 1107.
[2] Rathke, *Ann.*, 1873, 167, 219.
[3] G. D. Ssychev, *J. Khim. Promisel.*, 1930, 7, 1168.
[4] Bassett, *Jahresb. fortschr. Chem.*, 1866, 495; Nekrassov, *op. cit.*
[5] H. Bassett, *Ann.*, 1864, 132, 54; Röse, *Ann.*, 1880, 205, 219.
[6] H. Hartel, *Ber.*, 1927, 60, 1841.
[7] Alexejevsky, *J. Khim. Promisel.*, 1931, 8, 50.

Chloropicrin reacts with mercaptans at the ordinary temperature, forming hydrochloric acid and the ester of orthonitro trithioformic acid :

$$3R.SH + CCl_3NO_2 = (R.S)_3—C—NO_2 + 3HCl.$$

The researches of Ray and Das [1] show that on heating, the reaction takes place very rapidly and nitrous gases are evolved :

$$2(R.S)_3—C—NO_2 \rightarrow (R.S)_3—C—O—C—(R.S)_3 + N_2O_3.$$

Later researches by Nekrassov,[2] however, have demonstrated that chloropicrin in these conditions behaves as an oxidising agent on the mercaptan, so that a disulphide of the formula R.S.S.R and also carbon monoxide and nitrogen are formed.

$$2(R.S)_3—C—NO_2 \rightarrow 3R—S—S—R + 2CO_2 + N_2.$$

In this reaction between chloropicrin and mercaptans, an intense yellowish-red colouration is produced, which appears as readily in presence of potassium mercaptide as with the free mercaptan. As an insoluble substance is formed, this reaction may be employed for the detection of chloropicrin (see p. 178).

Chloropicrin oxidises hydrazine [3] even at the ordinary temperature, evolving nitrogen. Tronov and Gershevich [4] have studied the velocity of the reaction between chloropicrin and hydrazine in various solvents (alcohol, ether, carbon disulphide, etc.).

By the action of the sodium salts of the arylarsenious or alkylarsenious acids on chloropicrin in alcoholic solution, a reaction takes place which is first gentle and then very violent and leads to the formation of the following compounds [5] :

$$R\text{-}As\begin{smallmatrix}ONa\\ONa\end{smallmatrix} + CCl_3NO_2 = NaCl + \begin{smallmatrix}R\\NO_2Cl_2C\end{smallmatrix}\!\!>As\begin{smallmatrix}{=}O\\ONa\end{smallmatrix}$$

$$\begin{smallmatrix}R\\NO_2Cl_2C\end{smallmatrix}\!\!>As\begin{smallmatrix}{=}O\\ONa\end{smallmatrix} + 2\,NaOH = RAs\begin{smallmatrix}ONa\\{=}O\\ONa\end{smallmatrix} + CNaCl_2NO_2 + H_2O$$

Much data has been accumulated on the behaviour of chloropicrin in contact with metals. According to Ireland,[6] chloropicrin attacks steel slightly and copper and lead very energetically. American publications, however, assert that chloropicrin attacks all metals. The corrosion of metals is confined to superficial

[1] Ray and Das, *J. Chem. Soc.*, 1919, **115**, 1308 ; 1922, **121**, 323.
[2] Nekrassov and Melnikov, *Ber.*, 1929, **62**, 2091.
[3] A. K. Macbeth and J. D. Pratt, *J. Chem. Soc.*, 1921, **119**, 1356.
[4] Tronov and Gershevich, *J. Rush. fis. khim. obsc.*, 1928, **60**, 171.
[5] Jakubovich, *J. prakt. Chem.* (N.F.), 1933, **138**, 159.
[6] Ireland, *Medical Aspects of Gas Warfare*, Washington, 1926, 208

staining, a layer being formed which protects the metal from further corrosion.

Chloropicrin is one of the war gases most easily held back by active carbon.[1]

Fibrous materials absorb relatively little chloropicrin vapour and are not changed in resistance or colour. The absorbed chloropicrin may usually be removed by a current of dry air.[2]

Chloropicrin in vapour form strongly irritates the eyes. According to American observations (Fries), a man's eyes are closed after 3–30 seconds' exposure to an atmosphere containing 2–25 mgm. chloropicrin per cu. m. of air. At a concentration of 19 mgm. per cu. m. the eyes commence to lachrymate [3] and the limit of insupportability is about 50 mgm. per cu. m.

Besides its irritant action, chloropicrin has a toxic and asphyxiating action. The mortality-product is 20,000 according to Prentiss,[4] and according to Ferri is 12,000 for dogs and cavies,[5] and to Ritlop 15,000 to 20,000 for cats.[6]

3. Tetrachloro dinitroethane (M.Wt. 258)

$$\begin{array}{c}CCl_2NO_2\\ |\\ CCl_2NO_2\end{array}$$

This substance was first prepared by Kolbe,[7] who did not, however, succeed in determining its physical and chemical characteristics. It was later obtained by Biltz,[8] by the action of fuming nitric acid, or a mixture of nitric acid and concentrated sulphuric acid, on tetrachloroethylene.

It may also be obtained by the action of anhydrous nitrogen peroxide on tetrachloroethylene at 10–12 atmospheres and 60° to 80° C. for 3–6 hours (Biltz).

Laboratory Preparation (Biltz)

5 gm. tetrachloroethylene and about 8 gm. nitrogen peroxide are placed in a glass tube which is sealed off in the blowpipe and then heated at 100° C. for about 3 hours. After cooling, the tube is opened, the contents poured into a basin and the excess nitrogen peroxide allowed to evaporate off at room temperature. The solid white residue is then redissolved in warm

[1] H. S. Harned, *J. Am. Chem. Soc.*, 1920, **42**, 372 ; Herbst, *Biochem. Z.*, 1921, **115**, 204.
[2] Alexejevsky, *J. Prikl. Khim.*, 1929, **1**, 184.
[3] D. Kiss, *Z. ges. Schiess-Sprengstoffw.*, 1930, **25**, 269, 300.
[4] A. Prentiss, *Chemicals in War*, New York, 1937, 16.
[5] Ferri and Madesini, *Giorn. di Medicina Militare*, 1936.
[6] Ritlop, *Z. ges. Exp. Med.*, 1930, **106**, 206.
[7] H. Kolbe, *Ber.*, 1869, **2**, 326.
[8] H. Biltz, *Ber.*, 1902, **35**, 1529.

described previously, is provoked by finely divided solid particles, which on liberation in the air form true smokes and are known as the "*toxic smokes*." Phenyl dichloroarsine is an exception, not being a smoke.

Most of the aliphatic and aromatic arsines employed during the war of 1914–18 were substances which had been known for some time. The only new substances are the chlorovinyl arsines and phenarsazine chloride, of whose practical efficiency somewhat conflicting opinions are still held.

The fact that during the war only the compounds mentioned above were actually used does not indicate that they were superior to others which have been prepared and studied. Nevertheless, it is probable that preference will be given to those substances whose range of application is known, without using compounds of uncertain scope.

(A) ALIPHATIC ARSINES

The aliphatic arsines are substances which are generally liquid and oily, have a not unpleasant odour, are somewhat miscible with water, but are all more or less rapidly hydrolysed as follows:

$$\mathrm{R{-}As}\left\langle\begin{matrix}\mathrm{Cl}\\ \mathrm{Cl}\end{matrix}\right. + \left.\begin{matrix}\mathrm{H}\\ \mathrm{H}\end{matrix}\right\rangle\mathrm{O} = \mathrm{R{-}AsO} + 2\,\mathrm{HCl}$$

These substances, though more powerfully toxic than the aromatic arsines, are of minor importance because of their rapid diffusion in the air without forming aerosols.

Even the chlorovinyl arsines, although they are easily prepared, do not seem to be sufficiently aggressive in their action to replace the aromatic arsines. According to several authorities,[1] experiments on the methods of military application of the chlorovinyl arsines have been abandoned even in America.

Of the aliphatic arsines, only ethyl dichloroarsine has been widely employed as a war gas and is considered as the typical substance for use in projectiles. Methyl dichloroarsine is classed by some German authors [2] as a substance which was studied in the post-war period, but according to an American authority it was actually employed by the Allies towards the end of the war, though only in small quantity.[3]

Since the war, various other compounds of similar properties and method of preparation have been prepared and studied.

[1] Hanslian, *Der Chemische Krieg*, Berlin, 1927, 62.
[2] H. Muller, *Die Chemische Waffe*, Berlin, 1932, 111.

For instance, dimethyl chloroarsine (b.p. 106·5° to 107° C.), dimethyl bromoarsine[1] (b.p. 128° to 129° C.), dimethyl fluoroarsine,[2] methyl dicyanoarsine[3] (m.p. 115·5° to 116·5° C.), ethyl dibromoarsine, etc. All of these have aggressive properties inferior to those of methyl dichloroarsine.

Homologues of methyl dichloroarsine have also been prepared:

n-*Butyl-dichloroarsine*,[4] $C_4H_9AsCl_2$, obtained by the action of hydrochloric acid on *n*-butyl arsenic acid in the presence of sulphur dioxide, is an oily liquid boiling at 192° to 194° C.

Iso-*amyl dichloroarsine*,[5] $C_5H_{11}AsCl_2$, obtained by the action of phosphorus trichloride on *iso*-amyl arsenic acid, is a liquid boiling at 88·5° to 91·5° C. at 15 mm. mercury pressure.

This latter substance has great irritant power (Liebermann).

1. Methyl Dichloroarsine (M.Wt. 161)

$$\mathrm{CH_3-As}\left\langle\begin{matrix}\mathrm{Cl}\\ \mathrm{Cl}\end{matrix}\right.$$

Methyl dichloroarsine was prepared by Bayer[6] in 1858 by two different methods:

(*a*) By the decomposition of cacodyl trichloride at 40° to 50° C.

$$\begin{matrix}\mathrm{Cl}\diagdown\\ \mathrm{Cl{-}}\\ \mathrm{Cl}\diagup\end{matrix}\mathrm{As}\left\langle\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\right. \rightarrow \mathrm{CH_3As}\left\langle\begin{matrix}\mathrm{Cl}\\ \mathrm{Cl}\end{matrix}\right. + \mathrm{CH_3Cl}$$

(*b*) By the action of gaseous hydrochloric acid on cacodylic acid[7]:

$$\left.\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\right\rangle\mathrm{AsOOH} + 3\,\mathrm{HCl} = \mathrm{CH_3{-}As}\left\langle\begin{matrix}\mathrm{Cl}\\ \mathrm{Cl}\end{matrix}\right. + \mathrm{CH_3Cl} + 2\,\mathrm{H_2O}$$

Methyl dichloroarsine may also be obtained by treating dimethyl arsine with chlorine[8]:

$$\left.\begin{matrix}\mathrm{CH_3}\\ \mathrm{CH_3}\end{matrix}\right\rangle\mathrm{As{-}H} + 2\,\mathrm{Cl_2} = \mathrm{CH_3As}\left\langle\begin{matrix}\mathrm{Cl}\\ \mathrm{Cl}\end{matrix}\right. + \mathrm{CH_3Cl} + \mathrm{HCl}$$

[1] Steinkopf and Schwen, *Ber.*, 1921, **54**, 1454.
[2] Bunsen, *Ann.*, 1841, **37**, 38.
[3] Gryszkiewicz and Trochimovsky, *Bull. soc. chim.*, 1927, **41**, 1323.
[4] Quick and Adams, *J. Am. Chem. Soc.*, 1922, **44**, 805; Hanzlik, *J. Pharmac.*, 1919, **14**, 221.
[5] Steinkopf and Mieg, *Ber.*, 1920, **53**, 1015.
[6] Bayer, *Ann.*, 1858, **107**, 269.
[7] Zapp[illegible]

or, according to Auger,[1] by bringing about the reaction between methyl arsenic acid and phosphorus trichloride, which both reduces and chlorinates:

$$CH_3\text{-}As\begin{cases}OH\\ O\\ OH\end{cases} + PCl_3 \rightarrow HPO_3 + CH_3As\begin{cases}Cl\\ Cl\end{cases} + HCl$$

It is easily understood that this reaction, though convenient enough for the laboratory preparation of methyl dichloroarsine, is not suitable for its industrial manufacture because of the difficulty of procuring large quantities of the raw materials. The lack of an easy and simple method of manufacture may be considered as one of the principal causes which prevented methyl dichloroarsine from being employed as a war gas until the very end of the war, when only the Americans succeeded in producing it on an industrial scale by a simple method.

The method used by the Americans[2] commenced with sodium arsenite and dimethyl sulphate, and proceeded by the following stages:

(1) Methylation of the sodium arsenite with dimethyl sulphate[3]:

$$Na_3AsO_3 + \begin{matrix}CH_3\\ CH_3\end{matrix}\Big\rangle SO_4 = \begin{matrix}CH_3\\ Na\end{matrix}\Big\rangle SO_4 + CH_3As\begin{cases}ONa\\ O\\ ONa\end{cases}$$

(2) Reduction of the sodium methyl arsenate with sulphur dioxide, after acidification:

$$CH_3\text{-}As\begin{cases}ONa\\ O\\ ONa\end{cases} + SO_2 = Na_2SO_4 + CH_3\text{-}As{=}O$$

(3) Chlorination of the methyl arsenious oxide with hydrochloric acid:

$$CH_3As{=}O + 2\,HCl = CH_3As\begin{cases}Cl\\ Cl\end{cases} + H_2O$$

LABORATORY PREPARATION

In the laboratory, methyl dichloroarsine may be prepared by the method indicated above.[4]

100 gm. arsenious oxide are placed in a wide-mouthed glass flask of 1 litre capacity, a solution of 120 gm. sodium hydroxide in 150 gm. water is added and the whole heated on a water-bath

[1] AUGER, *Compt. rend.*, 1906, **142**, 1151.
[2] UHLINGER and COOK, *J. Ind. Eng. Chem.*, 1919, **11**, 105.
[3] *D.R.P.* 404580/March 15th, 1923.
[4] NENITZESCU, *Antigaz*, 1929, No. 2.

at 80° C. until the arsenious oxide is completely dissolved. Then, without heating, but stirring vigorously with a mechanical agitator, 64 gm. dimethyl sulphate are added little by little. The reaction between sodium arsenite and dimethyl sulphate is highly exothermic and the rate of addition of the latter should be so regulated that the temperature does not rise above 85° C.

When all the dimethyl sulphate has been added, the flask is fitted with a reflux condenser and the contents boiled for 2 hours. The sodium salt of methyl arsenic acid is obtained. It is allowed to cool and a small amount of potassium iodide is added, after which a current of sulphur dioxide is passed through the liquid until it is saturated (about 6 hours). The mixture is again boiled under reflux for about an hour; during this period, an oily substance consisting of methyl arsenious oxide deposits at the bottom of the flask, where it is saturated with a current of gaseous hydrochloric acid, while the flask is cooled externally. On attaining complete saturation, the flask is connected with a Liebig's condenser and the liquid distilled. Much hydrochloric acid is evolved at first; later a mixture of hydrochloric acid and methyl dichloroarsine distils over. The distillation is continued until no more oily liquid condenses. The distillate is placed in a separatory funnel and the oily layer separated and distilled.

INDUSTRIAL MANUFACTURE

A diagram of the American plant for the manufacture of methyl dichloroarsine is shown as Fig. 15.

The reaction takes place in a Pfaudler kettle *A* of about 100 gallons capacity, which is double-walled to allow of steam-heating and fitted with a mechanical agitator *F*. At the top of the lid two three-way cocks *R* and *R'* are fitted. The cock *R* serves for the introduction of the reactants and is connected with a long leaden tube which reaches almost to the bottom. This cock also connects both with the receiver *C* containing sodium arsenite, and with the two cylinders *DD'* of sulphur dioxide, with a pipe *O* through which the dimethyl sulphate enters and also with a smaller Pfaudler vessel *B*, of about 50 gallons capacity, in which the hydrochloric acid is prepared. The sulphuric acid which is used for preparing the hydrochloric acid is contained in the vessel *G* which is fed from the storage vessel *E* by means of a pump.

The three-way cock *R'* serves to carry off the reaction products and leads one way to a water-cooled condenser *M* and the other to a reflux condenser *P*, consisting of a lead coil contained in an iron cylinder full of ice and water, and leading to two sight bottles, *I* and *L*, by means of which any escape of gas from the apparatus may be observed.

A solution of sodium arsenite is first prepared in the container *C* by dissolving 42 kg. arsenious oxide in a solution of 64 kg. of NaOH in 188 kg. water. When it has completely dissolved the solution is introduced into the Pfaudler kettle *A* and then 64 kg. methyl sulphate are added through the pipe *O*, maintaining the temperature at about 85° C. The completion of the conversion

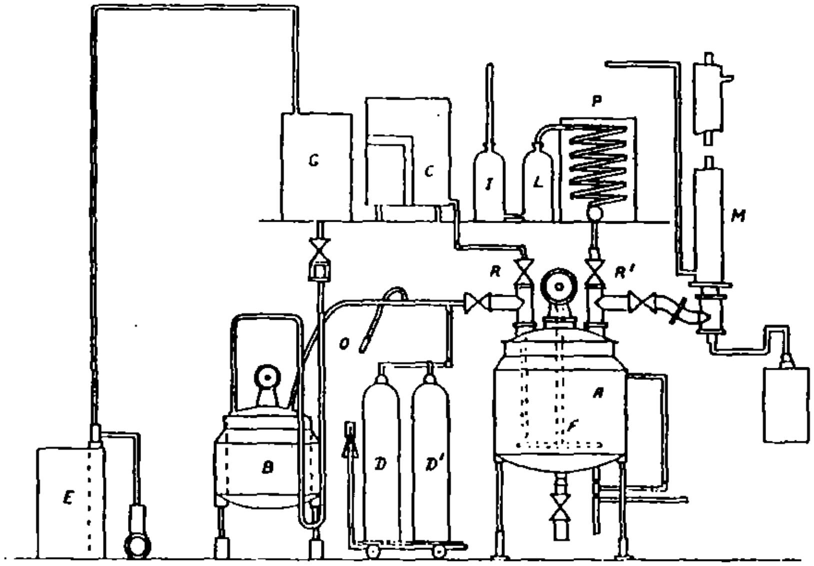


FIG. 15.

of the sodium arsenite into sodium methyl arsenate is shown by a drop in temperature. When this reaches 50° to 55° C. a current of sulphur dioxide is introduced from the cylinders *D* and *D'* and bubbles through the reaction product, which is maintained at 65° C., until complete saturation is attained and the reduction to methyl arsenious oxide complete. A current of gaseous hydrochloric acid is then passed in through the cock *R* to complete saturation, and finally the mixture is distilled.

The distillate is collected in a separatory vessel, and the oily layer dried with calcium chloride and fractionally distilled from an oil-bath. The methyl dichloroarsine passes over between 129° and 133° C.

PHYSICAL AND CHEMICAL PROPERTIES

Methyl dichloroarsine is a mobile, colourless liquid which has a characteristic odour and does not fume in the air.

It boils at 37° C. at 25 mm.,[1] at 55·5° C. at 50 mm.,[2] at 72·1° C. at 100 mm.,[2] at 89·1° C. at 200 mm.[2] and at 132° to 133° C. at ordinary pressure. Its melting point is −42·5° C. (Gibson) and its specific gravity 1·838 at 20° C. It has a vapour density of 5·5 and a coefficient of thermal expansion of 0·00102.

The vapour tension at a temperature *t* may be calculated from the formula (see p. 5).

$$\log p = 8{\cdot}6944 - \frac{2281{\cdot}7}{273 + t}$$

The values of the vapour tension at the following temperatures are[3]:

TEMPERATURE ° C.	VAPOUR TENSION *mm. mercury*
− 15	0·67
0	2·17
15	5·94
25	10·83
35	19·33

The volatility of methyl dichloroarsine at 20° C. is 74,900 mgm. per cu. m. of air.

It dissolves in water (1 gm. in 1,000 ml. water), being rapidly hydrolysed according to the equation[4]:

$$CH_3AsCl_2 + H_2O = CH_3AsO + 2HCl.$$

It is, however, easily soluble in the common organic solvents.

In contact with alkaline solutions, methyl dichloroarsine is quantitatively decomposed:

$$CH_3AsCl_2 + 2NaOH = CH_3AsO + 2NaCl + H_2O,$$

forming methyl arsenious oxide, as with water. This oxide is crystalline and colourless, has an odour of asafœtida and melts at 95° C. Its density is 2·48 and it is soluble in water, alcohol, ether and benzene and readily volatile in steam.[5]

Solutions of methyl dichloroarsine in carbon disulphide when cooled to − 10° C., easily absorb chlorine forming large crystals of methyl tetrachloroarsine, which decompose at 0° C. into methyl chloride and arsenic trichloride[6]:

$$CH_3AsCl_2 + Cl_2 \rightarrow CH_3As{-}Cl_4 \rightarrow CH_3Cl + AsCl_3.$$

[1] HERBST, *Kolloidchem. Beihefte*, 1926, **23**, 313.
[2] GIBSON and JOHNSON, *J. Chem. Soc.*, **1931**, 2520.
[3] BAXTER and BEZZENBERGER, *J. Am. Chem. Soc.*, 1920, 42, 1386.
[4] ADAMS, *Private communication*; RAIZISS and GAVRON, *Organic Arsenical Compounds*, New York, 1923, 41.
[5] RAIZISS and GAVRON, *op. cit.*
[6] BAYER, *Ann.*, 1858, **107**, 281.

Methyl dichloroarsine reacts with bromine water, forming methyl arsenic acid :

$$CH_3As\text{-}Cl_2 + H_2O = CH_3AsO + 2\ HCl$$

$$CH_3AsO + 2\ H_2O + Br_2 = CH_3AsO(OH)_2 + 2\ HBr$$

Methyl arsenic acid forms acicules with a melting point of 159° C. It is also obtained by the action of hydrogen peroxide on methyl dichloroarsine.[1]

Like all the halogenated arsines, gaseous ammonia converts it quantitatively into methyl arsinimide,[2] $CH_3As{=}NH$. This forms crystals which have an irritating odour and vesicant power and melt at 205° C.

In dry ether solution, methyl dichloroarsine does not react with magnesium, though in presence of water the reaction is violent : methyl arsine, hydrogen, methane and a compound, $(CH_3As)_4$, are formed. Zinc reacts similarly.[3]

With hydrogen sulphide, methyl arsenious monosulphide is formed (Bayer) :

$$CH_3AsCl_2 + H_2S = CH_3AsS + 2HCl.$$

This compound forms acicular crystals or small prisms with melting point 110° C. A detection reaction for the primary arsines is based on this sulphide formation[4] (see p. 328).

Aqueous solutions of methyl dichloroarsine reduce ammoniacal silver nitrate solutions (Nametkin).

Methyl dichloroarsine reacts with acetylene in presence of anhydrous aluminium chloride, forming a mixture of[5] :

(i) β chlorovinyl methyl chloroarsine of the formula

$$CH_3\text{-}As\begin{cases} Cl \\ CH{=}CH\cdot Cl \end{cases}$$

This is a liquid with a boiling point of 112° to 115° C. at 10 mm. mercury pressure, which behaves chemically in a similar manner to methyl dichloroarsine. It has a lesser irritant power, but has a vesicant action on the skin, producing blisters which are difficult to heal.

[1] Backer and coll., *Rec. trav. Chim.*, 1935, **54**, 186.
[2] Ipatiev and coll., *Ber.*, 1929, **62**, 598.
[3] Zappi, *Bull. soc. chim.*, 1918, **23**, 322.
[4] S. Nametkin and W. Nekrassov, *Z. anal. Chem.*, 1929, **77**, 285.
[5] Das Gupta, *J. Ind. Chem. Soc.*, 1936, **13**, 305.

(ii) $\beta\beta'$ dichlorovinyl methylarsine

$$CH_3\text{-}As\begin{cases} CH{=}CHCl \\ CH{=}CHCl \end{cases}$$

a liquid, with b.p. 140° to 145° C. at 10 mm. mercury pressure, having physiopathological properties similar to the preceding.

Dry methyl dichloroarsine does not attack iron or zinc (Prentiss).

The lower limit of irritation is 2 mgm. per cu. m. of air (Müller). The maximum concentration which a normal man can breathe for a period not greater than 1 minute is 25 mgm. per cu. m. of air (Lustig). The lethal index is 3,000 according to Müller and 5,600 for 10 minutes' exposure according to Prentiss.

The vapours of these substances have a vesicatory action of the same type as that of dichloroethyl sulphide.[1]

2. Ethyl Dichloroarsine (M.Wt. 175)

$$C_2H_5\text{—}As\begin{cases} Cl \\ Cl \end{cases}$$

Ethyl dichloroarsine was prepared by La Coste[2] in 1881 by acting on mercury diethyl with arsenic trichloride :

$$2\ AsCl_3 + Hg(C_2H_5)_2 = 2\ C_2H_5As\begin{cases} Cl \\ Cl \end{cases} + HgCl_2$$

It may also be obtained by heating ethyl arsine in a closed tube with mercuric, arsenic, antimony or stannous chloride.[3]

$$C_2H_5AsH_2 + 2HgCl_2 = C_2H_5AsCl_2 + 2Hg + 2HCl,$$

or by the decomposition of 10 ethyl 5·10 dihydrophenarsazine with gaseous hydrochloric acid[4] :

$$C_2H_5\text{-}As\begin{cases} C_6H_4 \\ C_6H_4 \end{cases}NH + 2\ HCl = C_2H_5AsCl_2 + (C_6H_5)_2\ NH$$

Ethyl dichloroarsine was employed in March, 1918, by the Germans, being considered suitable for replacing dichloroethyl sulphide in offensive operations because of its immediate vesicant effect and its non-persistent character.

[1] Hanzlik, *loc. cit.*
[2] La Coste, *Ann.*, 1881, **208**, 33.
[3] Dehn, *Am. Chem. Jour.*, 1908, **40**, 88
[4] Gibson and Johnson, *J. Chem. Soc.*, 1931, 2518

Recently several arsenical derivatives of naphthalene have been prepared :

Naphthyl methyl chloroarsine : $\begin{matrix} C_{10}H_7 \\ CH_3 \end{matrix}\Big\rangle AsCl$

and *Naphthyl methyl fluoroarsine* : $\begin{matrix} C_{10}H_7 \\ CH_3 \end{matrix}\Big\rangle AsF$

The biological properties of these have not been reported in the literature.[1]

1. Phenyl Dichloroarsine (M.Wt. 223)

$$C_6H_5-As\Big\langle\begin{matrix} Cl \\ Cl \end{matrix}$$

Phenyl dichloroarsine was prepared in 1878 by La Coste and Michaelis[2] by passing the vapours of benzene and arsenic trichloride through a heated tube. The product obtained was impure with the diphenyl compound and could be purified by distillation or crystallisation only with some difficulty. The same workers later studied another method for its preparation.[3] This is more convenient and consists in heating mercury diphenyl to 250° C. with an excess of arsenic trichloride.

Phenyl dichloroarsine may also be obtained by heating triphenylarsine with arsenic trichloride in a closed tube to 250° C. for 30 hours[4] :

$$As(C_6H_5)_3 + 2AsCl_3 = 3C_6H_5AsCl_2,$$

or by heating phenyl mercuri-chloride with arsenic trichloride to 100° C. for 4–5 hours (Roeder and Blasi's method).[5]

Laboratory Preparation

Roeder and Blasi's method, mentioned above, is usually employed for the preparation. 50 gm. mercuric acetate are dissolved in 50 ml. acetic acid in a thick-walled flask. 100 ml. benzene, free from thiophene, are added and the mixture heated for 5 hours in a boiling water-bath. After cooling, the insoluble part is filtered off and washed well with benzene, and the filtrate is evaporated to a small volume. Phenyl mercuri-chloride is thus obtained. 30 gm. of this are weighed into a flask, 100 gm. arsenic trichloride added and heated on the water-bath to 100° C. for 4–5 hours. A viscous suspension is formed first and then this is suddenly converted into a brown liquid, while crystals separate below. After filtration, the filtrate is distilled under reduced pressure. The excess of arsenic chloride passes over first and then, at a much higher temperature, the phenyl dichloroarsine.

[1] Sporzynsky, *Roczniki Chem.*, 1934, **14**, 1293.
[2] La Coste and Michaelis, *Ber.*, 1878, **11**, 1883.
[3] La Coste and Michaelis, *Ann.*, 1880, **201**, 196.
[4] Michaelis and Reese, *Ber.*, 1882, **15**, 2876.
[5] Roeder and Blasi, *Ber.*, 1914, **47**, 2751.

Physical Properties

Phenyl dichloroarsine when pure is a colourless liquid which gradually turns yellow. At ordinary pressures it boils at 255° to 257° C. and at 14 mm. pressure at 124° C. At − 20° C. it solidifies to a microcrystalline mass. The specific gravity is 1·654 at 20° C.

Its vapour tension at temperature t may be calculated from the formula :

$$\log p = 9.150 - \frac{3164}{273 + t}$$

The vapour tension at 15° C. is 0·014 mm. and the volatility at 20° C. is 404 mgm. per cu. m. The coefficient of thermal expansion is 0·00073.

It is insoluble in water, but easily soluble in the common organic solvents.

Chemical Properties

Water. Phenyl dichloroarsine on treatment with water is hydrolysed to phenyl arsenious oxide :

$$C_6H_5AsCl_2 + H_2O = 2HCl + C_6H_5AsO.$$

This forms crystals melting at 142° C.[1] and is insoluble in water and ether but soluble in alcohol, benzene and chloroform. A polymer of phenyl arsenious oxide is also formed, probably a dimer, of the formula[2]

$$C_6H_5-As\Big\langle\begin{matrix} O \\ O \end{matrix}\Big\rangle As\cdot C_6H_5$$

which forms crystals melting at 210° to 220° C.

Alkali Hydroxides. Phenyl dichloroarsine is also hydrolysed by the action of alkali hydroxide solutions. The phenyl arsenious oxide in presence of excess alkali is converted to the salt of the corresponding phenyl arsenious acid :

$$C_6H_5AsO + 2\,NaOH = C_6H_5As\Big\langle\begin{matrix} ONa \\ ONa \end{matrix} + H_2O$$

[1] Blicke, *J. Am. Chem. Soc.*, 1930, **52**, 2946.
[2] Steinkopf and coll., *J. prakt. Chem.*, [illegible] **141**, 301.

This salt reacts with chloropicrin forming the sodium salt of phenyl arsenic acid [1]:

$$C_6H_5As\begin{matrix}\diagup ONa \\ \diagdown ONa\end{matrix} + CCl_3NO_2 = NaCl + \begin{matrix}C_6H_5\diagdown \\ NO_2Cl_2C\diagup\end{matrix}As\begin{matrix}\diagup\!\!\diagup O \\ \diagdown ONa\end{matrix}$$

$$\begin{matrix}C_6H_5\diagdown \\ NO_2Cl_2C\diagup\end{matrix}As\begin{matrix}\diagup\!\!\diagup O \\ \diagdown ONa\end{matrix} + 2NaOH = C_6H_5 . As(=O)(ONa)_2 + NaCCl_2NO_2 + H_2O.$$

Halogens. With chlorine and phenyl dichloroarsine, an additive compound is formed, tetrachloro phenylarsine. This decomposes into phenyl arsenic acid in the presence of moisture.

Bromine, however, forms no additive compound. By treatment of phenyl dichloroarsine with excess of bromine, the molecule is decomposed with formation of dibromobenzene, arsenic chlorobromide and hydrobromic acid,[2] as follows:

$$C_6H_5AsCl_2 + 2Br_2 = C_6H_4Br_2 + AsBrCl_2 + HBr.$$

Ammonia. By the action of gaseous bromine on phenyl dichloroarsine in benzene solution, phenyl arsenimide[3] is obtained:

$$C_6H_5AsCl_2 + 3NH_3 = C_6H_5AsNH + 2NH_4Cl.$$

This forms crystals melting at 26·5° C. and decomposes rapidly with formation of phenyl arsenious oxide by the action of water or even on exposure to moist air:

$$C_6H_5AsNH + H_2O = C_6H_5AsO + NH_3.$$

Phenyl arsenimide both dispersed in the air and in solution has a very irritant action on the skin.[4]

Amines. Primary and secondary amines, both of the aliphatic and aromatic series, react vigorously with phenyl dichloroarsine, giving compounds of the following types:

$$C_6H_5As\begin{matrix}\diagup NH\cdot R \\ \diagdown Cl\end{matrix} \quad \text{and} \quad C_6H_5As\begin{matrix}\diagup N(R)_2 \\ \diagdown Cl\end{matrix}$$

and liberating hydrochloric acid. With aniline, for example, a compound of the following structure is formed:

$$C_6H_5As\begin{matrix}\diagup NHC_6H_5 \\ \diagdown Cl\end{matrix}$$

This is readily hydrolysed by the action of moisture forming phenyl arsenious oxide and aniline hydrochloride.

[1] JAKUBOVICH, *J. pr. Ch.* (*N.F.*), 1933, **138**, 159.
[2] RAIZISS and GAVRON, *Organic Arsenical Compounds*, New York, 1923, 115.
[3] MICHAELIS, *Ann.*, 1902, **320**, 291.
[4] IPATIEV and coll., *Ber.*, 1929, **62**, 598

With diphenylamine, 10 chloro 5·10 dihydro phenarsazine is formed [1]:

$$C_6H_5AsCl_2 + NH(C_6H_5)_2 = NH\begin{matrix}\diagup C_6H_4 \diagdown \\ \diagdown C_6H_4 \diagup\end{matrix}AsCl + C_6H_6 + HCl$$

With tertiary aliphatic amines, additive products are formed; triethylamine, for instance, forms:

$$C_6H_5{-}As\begin{matrix}\diagup Cl \\ - Cl \\ \diagdown\!\!\diagdown N(C_2H_5)_3\end{matrix}$$

Hydrogen Sulphide. By the action of hydrogen sulphide on phenyl dichloroarsine in alcoholic solution, phenyl arsenious sulphide,[2] C_6H_5AsS, is produced in crystals melting at 152° C.,[2] or 174° to 176° C.[3] This reaction is very sensitive, and as the sulphide obtained is insoluble in water, its formation may be employed to detect small quantities of the arsine (0·05 mgm. in 1 ml. water).

Silver Cyanide. By prolonged boiling (5 hours) of silver cyanide with phenyl dichloroarsine in benzene solution, phenyl dicyanoarsine,[4] $C_6H_5As(CN)_2$, is formed as crystals with an odour which is both aromatic and also resembles hydrocyanic acid. It melts at 78·5° to 79·5° C., and is readily decomposed by water or even by damp air, with formation of phenyl arsenious oxide and hydrocyanic acid.

Acid Chlorides. Phenyl dichloroarsine, when treated with the aliphatic acid chlorides, *e.g.*, acetyl chloride, in carbon disulphide solution and in presence of aluminium chloride, forms acetophenone and arsenic trichloride [5]:

$$C_6H_5AsCl_2 + CH_3COCl = C_6H_5COCH_3 + AsCl_3.$$

With chloroacetyl chloride, chloroacetophenone is obtained [6]:

$$C_6H_5AsCl_2 + ClCH_2COCl = C_6H_5COCH_2Cl + AsCl_3.$$

Dimethyl Arsine. With dimethyl arsine a white crystalline product, $C_6H_5AsCl_2.(CH_3)_2AsH$, is formed, which is readily decomposed by the action of moisture.[7]

[1] BURTON and GIBSON, *J. Chem. Soc.*, **1926**, 464; GIBSON, *J. Am. Chem. Soc.*, 1931, **53**, 376.
[2] KRETOV, *J. Obscei Khim.*, Ser. A, 1931, **1**, 411.
[3] BLICKE, *J. Am. Chem. Soc.*, 1930, **52**, [illegible].
[4] GRYSKIEWICZ and coll., *Bull. soc. chim.*, 1927, **41**, 1323.
[5] MALINOVSKY, *J. Obscei Khim.*, Ser. A, 1935, **5**, 1355.
[6] GIBSON and coll., *Rec. trav. Chim.*, 1930, **49**, 1006.
[7] DEHN, *J. Am. Chem. Soc.*, [illegible]

Diphenyl Arsine. By the action of diphenyl arsine on phenyl dichloroarsine, arsenobenzene and diphenyl chloroarsine are formed [1]:

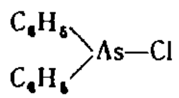
$$4\ C_6H_5AsCl_2 + 4\ (C_6H_5)_2AsH = \\ = 2\ C_6H_5\text{–}As\text{=}As\text{–}C_6H_5 + 4\ (C_6H_5)_2AsCl + 4\ HCl$$

Pure phenyl dichloroarsine does not attack iron.

Phenyl dichloroarsine was employed during the war of 1914–18 first by the Germans as a solvent for diphenyl cyanoarsine and later by the French in admixture with 40% of diphenyl chloroarsine under the name of "*Sternite.*"

Phenyl dichloroarsine is a lung irritant, a vesicant [2] and a lachrymatory. The maximum concentration which a normal man can support for not more than a minute is 16 mgm. per cu. m. of air (Flury). The mortality-product is 2,600 for 10 minutes' exposure (Prentiss).

2. Diphenyl Chloroarsine (M.Wt. 264·5)



Diphenyl chloroarsine was prepared in 1880 by La Coste and Michaelis[3] by heating mercury diphenyl with phenyl dichloroarsine:

$$2\ C_6H_5\text{–}As{<}^{Cl}_{Cl} + (C_6H_5)_2\ Hg = 2\ (C_6H_5)_2As\text{–}Cl + HgCl_2$$

Its employment in September 1917 was a great surprise to the Allies because of its peculiar physical properties which enabled it, when properly dispersed in the atmosphere, to pass through the respirator-filters then in use.

PREPARATION

Diphenyl chloroarsine may be prepared in various ways:

(1) By heating arsenic trichloride with benzene in presence of aluminium chloride:

$$2C_6H_6 + AsCl_3 = (C_6H_5)_2AsCl + 2HCl.$$

(2) By the decomposition of dichlorotriphenyl arsine, obtained by the action of chlorine on triphenyl arsine:

$$(C_6H_5)_3As{<}^{Cl}_{Cl} \rightarrow (C_6H_5)_2AsCl + C_6H_5Cl$$

[1] Blicke and Power, *J. Am. Chem. Soc.*, 1932, **54**, 3353.
[2] Hanzlich, *loc. cit.*
[3] Michaelis and La Coste, *Ann.*, 1880, **201**, 219.

(3) By the action of phenyl magnesium bromide on arsenious oxide. Triphenyl arsine is obtained at the same time.[1]

(4) By the reaction between phenyl dichloroarsine and diphenyl arsine [2]:

$$4\ C_6H_5AsCl_2 + 4\ (C_6H_5)_2AsH \rightarrow 4\ (C_6H_5)_2AsCl + \\ 2\ C_6H_5As\text{=}AsC_6H_5 + 4\ HCl$$

(5) By the action of arsenic trichloride on lead tetraphenyl in toluene solution [3]:

$$AsCl_3 + (C_6H_5)_4Pb = (C_6H_5)_2AsCl + (C_6H_5)_2PbCl_2.$$

During the war the Allies, in order to obtain rapid production of diphenyl chloroarsine, followed the method of Michaelis,[4] modified by Morgan and Vining.[5] This method consists in preparing triphenyl arsine from chlorobenzene and arsenic trichloride, in the presence of metallic sodium:

$$3C_6H_5Cl + AsCl_3 + 6Na = (C_6H_5)_3As + 6NaCl,$$

and then heating this substance with more arsenic trichloride:

$$2(C_6H_5)_3As + AsCl_3 = 3(C_6H_5)_2AsCl.$$

The Germans, however, used an entirely different process (see p. 306), based on the reaction between the diazonium salts and sodium arsenite which Bart had studied for the first time in 1912.[6]

LABORATORY PREPARATION

The preparation of diphenyl chloroarsine in the laboratory [7] is most conveniently carried out by Pope and Turner's [8] modification of the method of Michaelis.

57 gm. sodium cut into slices are placed in a round-bottomed flask fitted with a reflux condenser and covered with 300 ml. benzene containing 1–2% ethyl acetate (which catalyses the reaction). After allowing this mixture to stand for ½ hour (in order to activate the metal) 136 gm. chlorobenzene and 85 gm. arsenic chloride are slowly added. After a few minutes the reaction is considerably accelerated, and if necessary the flask should be cooled externally with a freezing mixture. It is then

[1] Blicke and Smith, *J. Am. Chem. Soc.*, 1929, **51**, 1558.
[2] Blicke and Power, *J. Am. Chem. Soc.*, 1932, **54**, 3353.
[3] Goddard and coll., *J. Chem. Soc.*, 1922, **121**, 978.
[4] Michaelis and Reese, *Ber.*, 1882, **15**, 2876.
[5] Morgan and Vining, *J. Chem. Soc.*, 1920, **117**, 780.
[6] Bart, *D.R.P.* 250,264; Schmidt, *Ann.*, 1920, **421**, 159.
[7] Nenitzescu, *Antigaz*, 1929, No. 2
[8] Pope and Turner, *J. Chem. Soc.*, 1920, **117**, [illegible]

AD

STUDIES OF ENVIRONMENTAL FATES OF DIMP AND DCPD

Final Report

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September 1979

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Project Officer: J. J. Barkley
Contract No. DAMD 17-78-C-8053
SRI Project LSU-7551

SRI International
Menlo Park, California 94025

EXECUTIVE SUMMARY

The role of photochemical and microbiological transformation processes in determining the environmental fates of diisopropyl methylphosphonate (DIMP) and dicyclopentadiene (DCPD) was investigated.

DIMP was unreactive to both direct and indirect photolysis in distilled and natural waters. This indicates that photolysis is not an important process for DIMP in aquatic systems. Biotransformation of DIMP also was not observed in natural waters after we attempted to acclimate microorganisms. Biotransformation of DIMP was slow in soil at 25°C and nearly nonexistent at 10°C. A half-life of more than 2 years is predicted for the biotransformation of DIMP to CO_2 in soil.

DCPD underwent photolysis only in the presence of natural water sensitizers. A half-life of more than 76 days was estimated. Biotransformation of DCPD was very slow in both soil and natural waters. Environmental half-lives for conversion to CO_2 by biotransformation were estimated to be 4 to 7 years in soil and 1 to 2 years in water at 25°C. Volatilization of DCPD from water was an important transport process, and a half-life of 5 days was estimated.

The results of attempts to photolyze DIMP at > 290 nm in both distilled and RMA waters showed no loss of parent compound, within an analytical error of ± 2%, after 232-hr reaction time, Table 2. The stability of DIMP to direct and indirect photolysis shows that photolysis is not important in determining the environmental fate of DIMP.

Table 2

RESULTS OF PHOTOLYSIS OF DIMP IN WATERS AT > 290 NM

Water	ΔT (hr)	DIMP Remaining (%)[a]
Distilled	89	100
North Bog-shallow	89	100
Distilled	232	100
North Bog-shallow	232	100

[a] Blank control maintained in dark gave 100% recovery

2. Biodegradation

Development of Acclimated Culture. The microorganisms in North Bog water and in RMA soil were grown in basal-salts medium with glucose (1 g/liter) and Difco yeast extract (0.1 g/liter). Then they were grown in shaker flasks with different concentrations of DIMP up to 100 ppm in basal-salts, glucose, and yeast-extract media. Comparisons of broth turbidity showed no growth inhibition, which indicated that a 100-ppm level of DIMP could be used to acclimate cultures.

The acclimation of DIMP biodegradation organisms with North Bog water collected in summer began in aerated 9-liter bottles with 10- and 3-ppm levels of DIMP, Tris buffer (pH 7.5), and $(NH_4)_2SO_4$. Autoclaved water with 10-ppm DIMP was used as a sterile control. The bottles were incubated at 25°C. Static bottles without buffer and ammonium salts were also incubated with DIMP (10 ppm) at 25° and 10°C. Analysis showed that DIMP was not biodegraded detectably during 12 weeks of incubation.

During this screening test, aliquots of water samples were inoculated into flasks containing Tris-buffer basal-salts medium with and without glucose (100 ppm); glucose (100 ppm) and yeast extract (20 ppm); glucose (100 ppm) and glycerol (100 ppm); or glucose, glycerol, and succinate (100 ppm each) as extra carbon sources. None of the flasks showed DIMP biodegradation.

The waters from the Palo Alto sewage plant aeration tank and from the pond near Searsville Lake, Woodside, California, were also tested in static bottles for the DIMP biodegradability with and without glucose, and with and without glycerol plus succinate. No DIMP biodegradation was observed.

To investigate the biodegradabilities of MP and IMP, the North Bog water in the 9-liter aerated bottles and Palo Alto aeration tank effluent water were inoculated into the flasks containing Tris-buffer basal-salts medium, glucose, glycerol, and succinate, with or without MP or IMP. The turbidity of the broth after 2 to 3 days in the flasks containing sugar and MP or IMP showed microbial growth, while that in the flasks containing only sugars (no phosphonate) showed very low turbidity. This result indicates that the microbes in North Bog water and in Palo Alto water could readily use MP or IMP as a phosphate source and split the carbon-phosphorus linkage, but could not use DIMP. When trimethylphosphate (TMP) was tested in place of MP in the above medium, it was also biodegraded.

When the North Bog water microbes were inoculated in the Tris-buffer basal-salt media with sugars and DIMP with added MP, IMP, or TMP, organisms grew with MP, IMP, or TMP as phosphate sources, but DIMP was not degraded. These compounds did not serve as cometabolic substrates or as enzyme inducers.

Isopropanol was added as a carbon source in the Tris-buffer basal-salts medium with DIMP. Although isopropanol was used by microorganisms as the sole carbon source in medium with phosphate, DIMP was not degraded. Like MP, IMP, and TMP, isopropanol did not serve as a cometabolic substrate or enzyme inducer.

North Bog water was collected again in January, and the acclimation test was repeated in static bottles. The water with and without Tris buffer, along with a sterile control, was incubated at 10°C. The water with Tris buffer was also incubated at 25°C. Again, chemical analysis showed no detectable DIMP biodegradation during 12 weeks of incubation.

Into biometer flasks containing Tris-buffer basal-salts medium, glucose, glycerol, 2 μCi of DIMP, and unlabelled DIMP (10 ppm), we inoculated North Bog water, Palo Alto water, and pond water microbes. Ten milliliters of 0.5N KOH solution was placed in the side arm. No radioactive $^{14}CO_2$ was observed in the KOH solutions during 6 weeks of incubation.

DIMP was biodegraded to CO_2 in RMA soil. To investigate whether this was caused by the presence of some nutrients in the soil, 20 g of RMA soil was extracted with 50 ml of boiling water, and 2.5 ml of the filtered supernatant was added to a 250-ml flask containing 50 ml of

Tris-buffer basal-salts medium with glucose and glycerol (200 ppm each). In another flask, 1 g of soil was added in place of the soil extract. Radiolabeled ^{14}C-DIMP (1.4 μCi) and DIMP (10 ppm) were added, and North Bog water was inoculated from the 9-liter bottle. The flask was closed with a rubber stopper equipped with a Teflon-lined screw-capped test tube, which has a hole under the rubber stopper so KOH solution can be placed in the tube to trap CO_2.[3] No evolution of $^{14}CO_2$ was found in these flasks, indicating that extra nutrients in the soil were not helping aqueous DIMP biodegradation.

Soil from the 13-week-old preliminary DIMP soil biodegradation flask, which contained acclimated microorganisms, was also inoculated into the above medium. No $^{14}CO_2$ evolution from methyl ^{14}C-DIMP was observed during 6 weeks of incubation. Thus, it appeared that environmental factors, not the microorganisms, are responsible for the persistence of DIMP in water.

The soil percolator of Goswami and Green[4] was used to acclimate the biodegradation culture from RMA soil. We then percolated 500 ml of an aqueous solution of DIMP (20 ppm) in Tris-buffer basal-salts medium with glucose and glycerol continuously through 50 g of RMA soil column. After 32 days 87% of the added DIMP still remained in the medium. This reduction may have been caused by adsorption, not by biodegradation. No further decrease was observed for 18 weeks.

In a parallel experiment, at 21 days the aqueous broth was inoculated into Tris-buffer basal-salts medium containing glucose, glycerol, and DIMP, IMP, or MP. Good growth was observed for media with MP or IMP, but no growth was observed in the medium with DIMP. After 11 days in DIMP medium, no significant reduction of DIMP concentration was noted.

Organisms reported to degrade IMP or other phosphonates were obtained from Dr. C. G. Daughton of M. Alexander's laboratory at Cornell University. The organisms--*Pseudomonas testosteroni* and strain No. 12[5,6] --were tested with Tris-buffer basal-salts medium and sugars with DIMP, IMP, and MP. They readily used MP and IMP as the sole phosphate source, but could not use DIMP.

Biodegradation Rate in Water. Since no biodegradation of DIMP in water samples was observed and no acclimated culture system developed, aquatic biodegradation studies were not conducted.

Soil Biodegradation. Preliminary soil biodegradation studies were begun in biometer flasks with RMA soil collected in August. The soil was a mixture of soils from Pit #1, Pit #4, and the North Bog. Radioactive methyl-^{14}C-DIMP (2.28 μCi in 1 ml of H_2O) was mixed into

50 g of the soil mixture, which originally contained 2.7 ppm DIMP. Sampled weekly, the KOH solution in the side arm was found to be trapping ^{14}C from volatilized DIMP and $^{14}CO_2$. The biometric flask containing sterile soil and ^{14}C-DIMP also had radioactivity in the KOH solution in the side arm.

The KOH solution from the flask with nonsterile soil was extracted with ethyl acetate, and the concentrated extract was spotted on a silica gel TLC plate and developed with 10% isopropanol/CH_2Cl_2 solvent. X-ray film radioautography showed that radioactivity in the extract was mainly from DIMP; no volatile metabolites were detected. The $^{14}CO_2$ in the KOH solution had to be precipitated with $BaCl_2$, the washed $BaCO_3$ acidified, and the CO_2 retrapped to make the $^{14}CO_2$ count. The $^{14}CO_2$ radioactivity was calculated as the percentage of ^{14}C originally added to the soil. The results are shown in Figure 1.

Figure 1 showed that DIMP was degraded to CO_2 by RMA soil microorganisms, but that biodegradation was very slow, with only 13.4% of the original activity being evolved as $^{14}CO_2$ after 34 weeks of incubation. Total ^{14}C removed in KOH solution during this period was 32% of the original ^{14}C. At this rate, it will take a year for the accumulated total ^{14}C to reach 50% and more than 2 years to achieve 50% evolution as $^{14}CO_2$.

We also tested a soil from SRI International grounds for DIMP degradation. The pattern of $^{14}CO_2$ evolution observed in SRI soil was similar to that in the RMA soil. To test whether the reductive generation of methane was possible, evolved gases were bubbled through a dodecane trap, which then was analyzed for methane by gas chromatography/mass spectrometry (GC/MS). Methane was not detected, indicating that the production rate was very low or that this mode of transformation is not occurring.

After soil samples were collected in January, the ultimate soil biodegradation testing was initiated with duplicate flasks at two temperature levels and at two DIMP levels. Soil collected in the summer and air dried was used for the 25°C incubation test, and soil collected in the winter was used for the 10°C incubation test. The soils collected in August and January had 2.9-ppm and 1.0-ppm levels of DIMP, respectively. Radiolabeled ^{14}C-DIMP (1.4 μCi) was added to the soils, with and without extra unlabeled DIMP (10 ppm).

Another flask containing additional DIMP (10 ppm) and ^{14}C-DIMP was inoculated with 1 ml of broth from the 8-week-old soil percolator at the start. It was again inoculated with 2 g of soil from the 22-week-old preliminary DIMP biodegradation test soil biometer flask after 4 weeks of incubation because the soil percolator did not acclimate the biodegradation organisms.

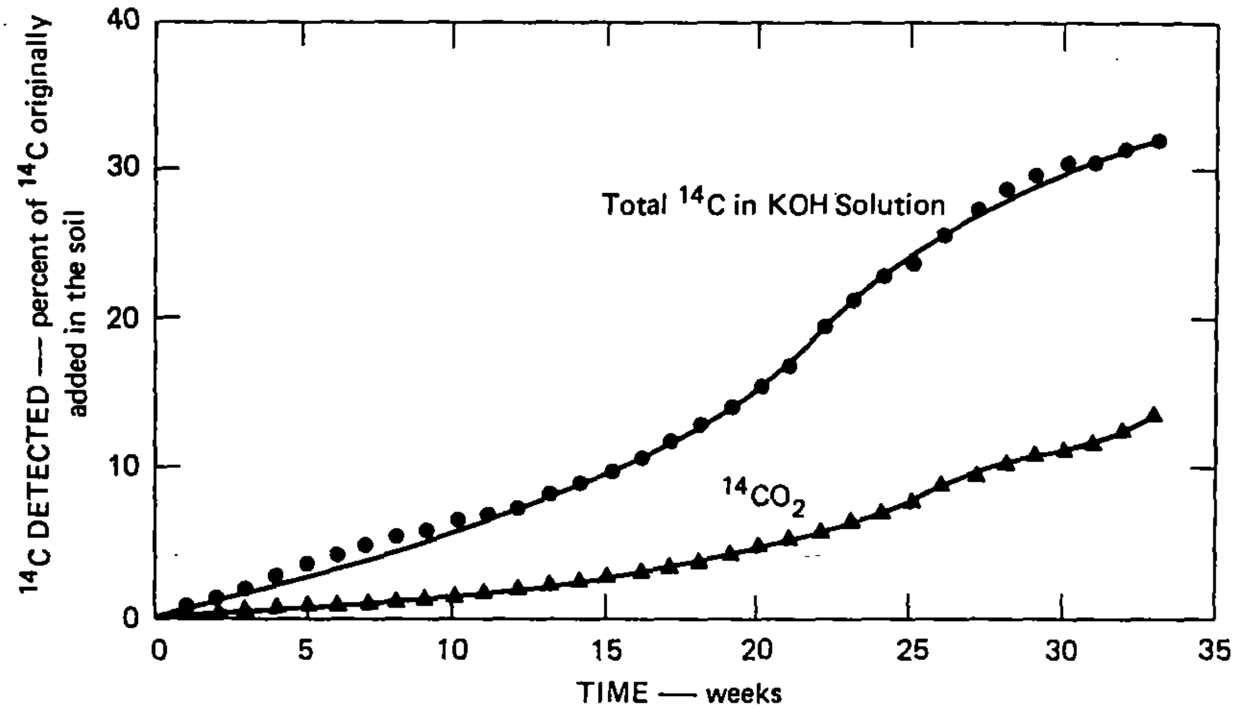

FIGURE 1 ACCUMULATED $^{14}CO_2$ AND TOTAL ^{14}C COUNT IN PRELIMINARY TEST FOR DIMP SOIL BIODEGRADATION

The $^{14}CO_2$ evolution during 17 weeks of incubation is shown in Figure 2. At 25°C, the percent of accumulated $^{14}CO_2$ from both the 2.9-ppm flasks and the 12.9-ppm flasks were about the same. The CO_2 production rates are therefore not a function of DIMP concentration. When soil was inoculated with the acclimated soil, the $^{14}CO_2$ evolution rate increased, and reached over 5% at 17 weeks; the soils without inoculation produced about 1.5%. At this rate, it will take more than 3 years to reach 50% mineralization in a noninoculated soil and more than 1 year in an inoculated soil.

The DIMP soil incubated at 10°C did not produce significant amounts of $^{14}CO_2$ (less than 0.1%). DIMP biodegradation in soil was almost completely halted at this temperature, and the evaporation loss was lower. The accumulated total ^{14}C counts in the KOH solution were about 15% of the added ^{14}C at 25°C and 3% at 10°C; it was 20% in the flask with acclimated soil at 25°C during 17 weeks of incubation.

Analytical Chemistry. The RMA soils and waters were analyzed for DIMP and its two primary hydrolysis products, IMP and MP, as well as phosphate ion, using capillary GC for all species and confirming phosphate by colorimetry.[7] A summary of results appears in Table 3. Components were identified by capillary gas chromatographic retention time and confirmed by GC/MS. A typical gas chromatographic profile of a sample extract appears in Figure 3.

Chemical Hydrolysis. The appearance of IMP and MP in RMA water suggested that catalytic hydrolysis could be occurring. To test this possibility, 100 ml of North Bog water containing 0.26 ppm of DIMP was refluxed for 1 hr and reanalyzed for DIMP. The recovery of DIMP was 98% of the original concentration, indicating that no catalytic processes are transforming DIMP in the environment.

D. Conclusions

Data for the photolysis of DIMP in distilled water and in a natural water sample showed no loss after 232 hr of photolysis with the Hg lamp filtered to exclude all wavelengths below 290 nm. Direct or indirect photolysis therefore is not important in aquatic systems.

Biodegradation of DIMP was not observed in natural waters incubated for 12 weeks or in aqueous medium incubated with acclimated soil microorganisms for 6 weeks. Therefore, we conclude that this transformation process also is not important in aquatic systems.

The methyl carbon in DIMP was observed to biodegrade to CO_2 very slowly at 25°C in soil, and almost no biodegradation was observed at 10°C. Thus, temperature variations will be important in estimating the persistence of DIMP in an environment such as that of RMA, and a half-life in excess of two years is predicted.

CHEMCYCLOPEDIA 97

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CHEMCYCLOPEDIA is published annually as a supplement to *Chemical & Engineering News* by the *American Chemical Society at 1155 16th Street, N.W.*, Washington, D.C. 20036, 1-202 872-4600. ACS assumes no responsibility for the statements and opinions advanced by contributors to its publications.

POSTMASTER. *Send address changes to* ACS Membership & Subscription Services, P.O. Box 3337, Columbus, Ohio 43210

VOLUME 15
1997

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DIHYDROXYALUMINUM SODIUM CARBONATE (16482-55-6)
Chattem Chemicals Inc. Dry powder, milled or densified grades. 55-gal drum. Antacid raw material.
Giulini Corp Powder grade. 55-gal drum. Antacid raw material.

2,4-DIHYDROXYBENZALDEHYDE (95-01-2)
F[illegible] Photo Film Co. Ltd. DHBA. 5-gal pail.
[illegible]rdwicke Inc.

4,5-[illegible]XY-1,3-BENZENE DISULFONIC ACID
[illegible]oulenc Organic Intermediates.

2,3-DIHYDROXYBENZOIC ACID (303-38-8)
F[illegible]nton Laboratories Inc. Crystsalline powder, research grade. 5-gal pail, 10-kg pail, lab quantities. Chemical intermediate.
E-MAIL. 70222.754@compuserve.com

2,6-DIHYDROXYBENZOIC ACID (303-07-1)
Spectrum Bulk Chemicals. Research, semibulk, and drum quantities.

2,4-DIHYDROXYBENZOPHENONE (131-56-6)
BASF Corp.
Cytec Industries Inc.
Neville-Synthese Organics. SYNTASE 100. Pale [illegible] powder grade. 200-lb drum. UV light ab[illegible] soluble in most organic solvents, compat[illegible] with most polymers, useful in polymers that require high-temperature processing and conversion.
Rhone-Poulenc Organic Intermediates.

2,5-DIHYDROXY-1,4-BENZOQUINONE
Spectrum Bulk Chemicals. Research, semibulk, and drum quantities.

4,4'-DIHYDROXYDIPHENYL SULFONE (80-09-1)
James River Specialty Chemicals. 93+% grade. 220-lb drums.

1,2-DIHYDROXYMETHYL ACETYLENE
Huls Aktiengesellschaft

6,7-DIHYDROXY-4-METHYLCOUMARINE
Jonas Chemical Corp.

4,5-[illegible]ROXY-2-METHYLMERCAPTOPYRIMIDINE
[illegible] Aktiengesellschaft

1,7-DIHYDROXYNAPHTHALENE
SST Corp.

2,6-DIHYDROXYNAPHTHALENE
SST Corp.

4,6-DIHYDROXY-5-NITROPYRIMIDINE
Interchem Corp.
SAF Bulk Chemicals.

3,4-DIHYDROXYPHENYLGLYCOL
Regis Technologies Inc. High-purity grade. Gram quantities. Store cold.

4,6-DIHYDROXY-2-PHENYLPYRIMIDINE
Huls Aktiengesellschaft

DI[illegible]XYPROPYL THEOPHYLLINE (Dyphylline)
BASF Fine Chemicals/BASF K&F Corp. Fine powder, 100- to 200-mesh grades. 50-kg drums.

2,4-DIHYDROXYPYRIDINE (626-03-9)
Vanguard Labs.

4,6-DIHYDROXYPYRIMIDINE (1193-24-4)
Huls Aktiengesellschaft
Interchem Corp.

5,7-DIHYDROXYTRYPTAMINE CREATININE SULFATE (39929-27-6)
Pharmasyn Inc.
Regis Technologies Inc. 99% purity grade. Gram quantities Pharmacological tool for investigating serotonin neurons and inducing chemical lesions in [illegible]

[illegible]DROXYTRYPTAMINE CREATININE SULFATE
Regis Technologies Inc. High-purity grade. Gram quantities.

***p*-DIIODOBENZENE (624-38-4)**
R.S.A. Corp.

2,5-DIIODOBENZOIC ACID (14192-12-2)
Deepwater Iodides Inc. 55-gal drum, 5-gal pail.
R.S.A. Corp.

4,4'-DIIODOBIPHENYL
SST Corp.

DIIODOHYDROXYQUINOLINE (83-73-8)
R S.A. Corp.

[illegible]METHANE (75-11-6)
[illegible]water Iodides Inc. 55-gal drum, 5-gal pail.
[illegible].A. Corp.

DIIODOMETHYL *p*-TOLYL SULFONE (20018-09-1)
ANGUS Chemical Co. AMICAL. Wettable powder, flowable powder forms

2,6-DIIODO-4-NITROPHENOL (305-85-1)
R.S.A. Corp.

1,3-DIIODOPROPANE (627-31-6)
Deepwater Iodides Inc. 55-gal drum. 5-gal pail.
R.S.A. Corp.

3,5-DIIODOSALICYLIC ACID
Acros Organics.
Spectrum Bulk Chemicals. Research, semibulk, and drum quantities.

DIIODOTYROSINE
R.S.A. Corp.

DIISOBUTYL KETONE (108-83-8)
Ashland Chemical Co., Industrial Chemicals & Solvents Div. Relatively slow evaporating solvent for nitrocellulose; useful in hot spray and multicolor formulations.
E-MAIL: csy@ashchem.com
INTERNET: http://www.ashchem.com
Eastman Chemical Co.
Union Carbide Corp. UCAR.

DIISOBUTYL MALEATE (14234-82-3)
Finetex Inc. Tank car, tank truck, 55-gal drum. Intermediate for sulfosuccinates.
MFG Chemical, Inc. Tank truck, 55-gal drum.

DIISODECYL PHTHALATE (26761-40-0)
Aristech Chemical Corp.
Ashland Chemical Co., Industrial Chemicals & Solvents Div. Provides permanent low-temperature flexibility in vinyls, has good resistance to migration and water extraction.
E-MAIL: csy@ashchem.com
INTERNET. http://www.ashchem.com
BASF Corp. PALATINOL DIDP. Stabilized, unstabilized grades. Tank car, tank truck. Plasticizer.
Primachem Inc.

DIISONONANOYL PEROXIDE (58499-37-9)
Elf Atochem North America Inc.
Elf Atochem North America, Organic Peroxides Div. LUPERSOL 219M75.

DIISONONYL ADIPATE (33703-08-1)
Aristech Chemical Corp.
BASF Corp. PALATINOL DNA. Tank car, tank truck.

DIISONONYL PHTHALATE (28553-12-0)
Aristech Chemical Corp.
Ashland Chemical Co., Industrial Chemicals & Solvents Div. 55-gal drum, bulk quantities. Used in flexible PVC formulations. Excellent low temperature and volatility characteristics. Used in automotive, film and sheeting, and plastisols.
E-MAIL: csy@ashchem.com
INTERNET. http://www.ashchem.com

DIISOPROPANOLAMINE (110-97-4)
Ashland Chemical Co., Industrial Chemicals & Solvents Div. Tank truck, 55-gal drum.
E-MAIL: csy@ashchem.com
INTERNET: http://www.ashchem.com
Huls Aktiengesellschaft

DIISOPROPYLAMINE (108-18-9)
Chem-Impex International, Inc.
Elf Atochem North America Inc. Tank car, tank truck, 55-gal drum, 5-gal pail. UN 1158.

DIISOPROPYLAMINOETHANOL (Diisopropylethanolamine)
Elf Atochem North America Inc. Tank car, tank truck, 55-gal drum, 5-gal pail. NA 1993.

***DIISOPROPYLAMINOETHYL CHLORIDE* HYCHLORIDE**
Interchem Corp.
Lonza Inc.

DIISOPROPYL AZODICARBOXYLATED
Allied Signal Inc., Engineered Materials Sector Liquid form. 110- and 441-lb drums.
CM Chemical Products Inc.

***m*-DIISOPROPYLBENZENE (99-62-7)**
Eastman Chemical Co.
Koch Chemical Co.

***p*-DIISOPROPYLBENZENE (100-18-5)**
Eastman Chemical Co.
Koch Chemical Co.

***N,N'*-DIISOPROPYLCARBODIIMIDE (693-13-0)**
Advanced ChemTech.
Chem-Impex International, Inc.
Lancaster Synthesis Inc.

1,3-DIISOPROPYLCARBODIIMIDE
SAF Bulk Chemicals.

DIISOPROPYLCHLOROSILANE
Boulder Scientific Co. Tank car, tank truck, 55-gal drum, 5-gal pail. Bulk supplier.
Gelest Inc. 55-gal drum, 1- and 5-gal pails.

***N,N'*-DIISOPROPYLDIAMIDOPHOSPHORYL FLUORIDE (371-86-8)**
Chemsyn Science Labs. MIPAFOX. High-purity *grades. Research quantities. Excepted quantity 49* CFR 173 4 Preferred selective inhibitor when measuring neurotoric esterase activity for the determination of neurotoxicity of organophosphorus compounds

DIISOPROPYLETHYLAMINE (7087-68-5)
Advanced ChemTech.
Austin Chemical Co. 55-gal drum, Commercial quantities Known as Hunig s base
Chem-Impex International, Inc.
Lancaster Synthesis Inc.
PPG Industries Inc., Fine Chemicals. Liquid form Tank car, tank truck, 55-gal drum.
Wilshire Chemical Co. Inc.
E-MAIL: WilshrChem@aol.com
INTERNET: http://users.aol.com/WilshrChem/Wi

***N,N*-DIISOPROPYLETHYLAMINE (7087-65-5)**
Austin Chemical Co. 55-gal drum. Known as Hunig's base.
Interchem Corp.
SAF Bulk Chemicals.
Spectrum Bulk Chemicals. Research, semibulk, an drum quantities.

DIISOPROPYLFLUOROPHOSPHATE (55-91-4)
Spectrum Bulk Chemicals. Research, semibulk, an drum quantities.

DIISOPROPYL KETONE
Huls Aktiengesellschaft

DIISOPROPYLMALONATE
Huls Aktiengesellschaft

DIISOPROPYL METHANE PHOSPHONATE (1445-75-6)
Lancaster Synthesis Inc.

DIISOPROPYLOCTYLSILANE
SAF Bulk Chemicals.

2,6-DIISOPROPYLPHENOL
Albemarle Corp.

2,6-DIOISOPROPYLPHENYL ISOCYANATE (28178-42-9)
Lancaster Synthesis Inc.

DIISOPROPYLPHOSPHORODITHIOIC ACID (107-56-2)
Zeneca Inc., Performance & Intermediate Chemicals. 85% min purity grade. 55-gal drum, bulk quantities. UN 2924, corrosive, flammable. Intermediate for pesticides, lubricant additives, and other industrial compounds.

DIISOPROPYL-*p*-TOLUIDINE
R.S.A. Corp.

DIKETENE (674-82-8)
Eastman Chemical Co. Liquid, assay 99.4% grades
Lonza Inc.
Wacker-Chemie GmbH

DILAURYL THIODIPROPIONATE (123-28-4)
Cytec Industries Inc. CYANOX LTDP. Flake grade 200-lb net drum. Secondary antioxidant for plastics
Hampshire Chemical Corp., Evans Chemetics Unit EVANSTAB 12. Flake form. 100- and 200-lb drums Nonhazardous. Secondary antioxidants for polyolefins FDA cleared.
Morton International Inc., Performance Chemicals CARSTAB DLTDP. Flake form. 100-lb fiber drum Secondary antioxidant for polyolefins and ABS FDA approved.
Witco Corp., Polymer Additives. 200-lb batch c container. Antioxidant.

DILTIAZEM HYDROCHLORIDE (33286-22-5)
Biomol Research Laboratories Inc. USP grade. K quantities
E-MAIL: info@biomol.com
INTERNET: http://www.biomol.com
Interchem Corp.
SST Corp.

DIMEDONE (126-81-8, 3471-13-4)
Lancaster Synthesis Inc.
Rhone-Poulenc Organic Intermediates.
Rhone-Poulenc Surfactants & Specialties.

DIMENHYDRINATE (523-87-5)
BASF Fine Chemicals/BASF K&F Corp. USP grade 25- and 50-kg drums.
Ganes Chemicals Inc.
Napp Technologies Inc.

DIMER ACIDS
Expo Chemical Co. Inc. Various grades including by product, also trimers Tank truck, 55-gal drum Component in corrosion inhibitors. Low cost alternative.
Unichema International. PRIPOL. Liquid form. Bulk drums.
Unichema North America. PRIPOL. Liquid form. Tar car, tank truck, 55-gal drum. Oleates, stearates, ca prylates, caprates, laurates, myristates, polami tates, and acetates.

DL-2,3-DIMERCAPTO-1-PROPANESULFONIC ACID, SODIUM SALT, MONOHYDRATE (4076-02-2)
Acros Organics.
Spectrum Bulk Chemicals. Research, semibulk, a drum quantities

meso-2,3-DIMERCAPTOSUCCINIC ACID (304-55-2)
Spectrum Bulk Chemicals. Research, semibulk, ar drum quantities.

2,5-DIMERCAPTO-1,3,4-THIADIAZOLE (1072-71-5, 64741-96-4)
R. T. Vanderbilt Co. Inc. VANCHEM DMTO. Dr powder form 100-lb fiber drums

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Sweet, D.V. (editor), 1987, *Registry of Toxic Effects of Chemical Substances (RTECS)*, 1985-1986 Edition, DHHS(NIOSH) Publication No. 87-114, prepared for the National Institute for Occupational Safety and Health under Contract No. 200-84-2768 by Advanced Engineering and Planning Corp., Inc., Rockville, Md.

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GAS WARFARE

THE CHEMICAL WEAPON,
ITS USE, AND PROTECTION AGAINST IT

BY

BRIGADIER GENERAL ALDEN H. WAITT

Chemical Warfare Service, U. S. Army

Revised edition, 1944

DUELL, SLOAN AND PEARCE
NEW YORK

Chlorine, the first gas to be used in modern chemical warfare is not likely to be met alone because it is so active chemically that protection against it can be improvised very easily and because other more toxic agents can be provided without difficulty. However, it may be mixed with phosgene in gas cylinders where its extremely high gas pressure and the fact that it is a gas even at low temperatures make it useful in providing the necessary pressure to force the more poisonous phosgene out of the cylinders.

Chlorine is an element which plays a very important part in chemical warfare since, either in a free or combined condition, it enters, somewhere, into the manufacture of practically all other chemical warfare agents. It is a heavy greenish-yellow gas which has a pungent, disagreeable odor and a very irritating effect upon the membranes of the upper air passages. It causes violent coughing immediately if small amounts are breathed. It is two and a half times as heavy as air. It is a gas at all temperatures that would obtain on the battlefield. It dissolves readily in water. It is extremely active chemically and combines with all the metals and with most all of the other elements. It is, therefore, extremely corrosive unless absolutely dry. When chlorine is thoroughly dry it may be stored in steel cylinders indefinitely. Chlorine is used in the manufacture of mustard gas, Lewisite, phosgene, and most other chemical agents. Chlorine compounds are important in protection against gas since certain of them, for example, chloride of lime (bleach), are used to destroy mustard gas.

One of the most effective choking gases used in the First World War was diphosgene. This substance not only is as poisonous as phosgene but has a marked tear-gas effect. Russian and German authorities state that it is more toxic than phosgene. The Germans used diphosgene in shells marked with a green cross and, hence, it was sometimes known as "green cross," although the official German name for the agent was perstoff. The British who also used it called it superpalite or diphosgene, and the French called it surpalite. It has a very imposing chemical name, trichlormethylchlorformate. It is a colorless, oily liquid with a peculiar odor. It breaks down under certain conditions to form two molecules of phosgene, which is the reason for its name. Except for the fact that it is a liquid under all field conditions and has an intense tear-gas effect, it can be thought of as very similar to phosgene, and no further description of it is needed here. It is an agent which is quite likely to be used whenever lung irritants are used. It would probably be employed in shells or bombs.

Although diphosgene must be classified as persistent, since it will remain at the point of release over ten minutes, it dissipates in the open in the summer in about fifteen minutes and in cooler weather within a half hour, so it is only very moderately persistent. It has not been used by our Army although it offers some advantages over the standard lung irritant, phosgene.

Another important lung irritant is chlorpicrin (PS), which also is an effective tear gas. PS is much more persistent than phosgene and is also less poisonous. It is classified as a moderately persistent agent since it has a persistency of about an hour in the summer in open country and twelve hours in the winter. The chemical name of chlorpicrin is trichlornitromethane or nitrochloroform. It gets the name of chlorpicrin because it is made commercially by the action of and chemical mortar shells. CNS is suitable for use in artillery and mortar shells and may be sprayed from tanks on airplanes to produce sudden and extremely high concentrations on the ground.

BBC (brombenzylcyanide) is the only tear gas that was manufactured by the Chemical Warfare Service in any quantity during World War I and only about five tons of it were made here. It was used in large amounts by the French, loaded in artillery shells. The French called it camite and gave it the code symbol CA. BBC is a heavy, oily, dark-brown liquid which has an odor like sour fruit. It is very persistent, lasting several days in the summer and several weeks in the winter. Although it is a more intense tear gas than CN and its action is more effective in low concentrations, it is not as satisfactory for military use since it has much less stability than CN. It attacks common metals with the exception of lead. In steel shell it rapidly corrodes the metal and in the process decomposes itself, losing its tear-gas properties. Artillery shells, therefore, must be lined with lead, glass, or porcelain if they are to contain BBC. The British have used BBC as a standard tear gas.

During World War I several other materials were used as tear gases. The principal lacrimator used by the British was SK (ethyliodoacetate). The Germans used T-Stoff (xylyl and benzyl bromide), a powerful lacrimator effective in concentrations of one volume in one million volumes of air, and K-Stoff (a brominated methyl-ethyl ketone also called B-Stoff) which was intense and quick-acting and somewhat less persistent than T-Stoff.

The French used a large number of materials with names such as tonite, cyclite, martonite, and bretonite. These compounds were all somewhat similar in their chemical nature and varied chiefly in the intensity of their effects.

Vomiting Gases or Irritant Smokes

When the chemists started their search for toxic chemicals for use in war, one of the earliest possibilities thought of was arsenic. Arsenic compounds are widely known for their poisonous nature of which commercial use is made. The only simple arsenic compound that showed any promise was arsine—highly poisonous and a gas. It proved to be too unstable and inflammable, however, to be of any use.

Investigation of the more complex arsenic compounds brought to light a number of possibilities and many of them were found to be useful in chemical warfare. The best known examples are: L (Lewisite), MD, ED (dick), DA, and DM. The Chemical Warfare Service up to the present time has adopted only three of these arsenic compounds as chemical agents: L, DA, and DM. L and ED have already been discussed as vesicants.

DA (Blue Cross) and DM (Adamsite) resemble each other closely. These two compounds are placed in a separate class among chemical agents—the vomiting gases or irritant smokes. They produce their effect by being liberated in the air as a smoke, as finely divided solid particles, and not as a vapor like phosgene, or as a mist like mustard.

The fact that these particles are solids, makes a lot of difference in our gas masks. The solid particles cannot be absorbed by the chemicals in the gas-mask canister as are gases and, therefore, must be filtered out mechanically. The finer the particle, the harder to filter it out and also the greater the irritant effect.

Munitions suitable for use	Mixed with CG and PS in cylinders and LP shells.
Marking on munitions	1 green band—CL gas.
Protection required	Gas mask.

CHLORPICRIN

Common name	Chlorpicrin (vomiting gas).
Chemical name	Trichlornitromethane (Cl_3CNO_2).
C. W. S. symbol	PS.
Persistency, summer	1 hour in open; 4 hours in woods.
Persistency, winter	12 hours in open; 1 week in woods.
Tactical classification	Harassing agent and casualty agent.
Physiological classification	Lung irritant and tear gas.
Odor in air	Sweetish, like fly paper.
Melting point	−69.2° C. (−92.4° F.).
Boiling point	112° C. (231.5° F.).
Volatility at 20° C. (68° F.)	165 oz./1,000 cu. ft. air.
Vapor pressure at 68° F.	18.28 mm. of mercury.
Vapor density compared to air	5.6.
Density of liquid at 20° C. (68° F.)	1.66
Solvents for	Chloroform, CG, chlorine.
Action on metals	Produces slight tarnish only.
Stability on storage	Stable for long periods in steel containers.
Action with water	Very slightly soluble.
Hydrolysis product	Hydrolyzes with difficulty.
Physiological action	Lacrimates, irritates nose and throat, produces nausea and lung irritation in order as concentration increases.

First Aid	Wash eyes with boric acid; keep patient warm and protect throat from infection.
Odor detectable at	0.007 oz./1,000 cu. ft. air.
Intolerable concentration	3 minutes' exposure; 0.02 oz./1,000 cu. ft. air.
Lethal concentration	10 minutes' exposure; 0.05 oz./1,000 cu. ft. air.
Method of neutralizing	Sodium sulfite solution.
Munitions suitable for use	Mixed with CN in artillery shells; air bombs, chemical mortar shell; airplane spray. Mixed with CG in LP shells.
Marking on munitions	2 green bands—PS gas.
Protection required	Gas mask.

DIPHOSGENE

Common name	Diphosgene.
Chemical name	Trichlormethylchlorformate ($Cl_3C\ COOCl$).
C. W. S. symbol	DP.
Persistency, summer	30 minutes.
Persistency, winter	2 hours.
Tactical classification	Casualty agent.
Physiological classification	Choking gas.
Odor	Smells like phosgene, but more irritating and choking.
Melting point	−57° C. (− 70.6° F.).
Boiling point	127° C. (260.6° F.).
Volatility at 20° C. (68° F.)	120 oz./1,000 cu. ft. air.
Vapor pressure at 20° C.	10.3 mm. of mercury.

Vapor density compared to air	6.9.
Density of liquid at 20° C. (68° F.)	1.65.
Action on metals	Same as phosgene.
Stability on storage	Stable in dry steel containers.
Action with water	Slowly hydrolyzes to form phosgene, HCl, and CO_2.
Physiological action	Burns lower breathing apparatus causing edema, irritates eyes.
First Aid	Same as phosgene.
Minimum irritating concentration	.005 oz./1,000 cu. ft. air.
Lethal concentration	Probably about the same as phosgene. German data, however, gives toxicity on 10-min. exposure .05 oz./1,000 cu. ft. air.
Method of neutralizing	Same as phosgene.
Munitions suitable for use	Artillery and mortar shell; LP shell.
Protection required	Gas masks.

IRRITANTS (EYES AND NOSE)

ADAMSITE

Common name	Adamsite*
Chemical name	Diphenylaminechlorarsine $(NH\ (C_6H_4)_2AsCl)$.
C. W. S. symbol	DM.
Persistency, summer	5 minutes in open from candles.
Persistency, winter	5 minutes in open from candles.
Tactical classification	Harassing agent.

Physiological classification	Sternutator; irritant smoke.
Odor in air	No pronounced odor.
Melting point	195° C. (383° F.).
Boiling point	410° C. (770° F.). Decomposes below boiling point.
Volatility at 20° C. (68° F.)	Negligible.
Vapor density compared to air	No vapor; disseminated as solid.
Density of solid 20° C. (68° F.)	1.65.
Solvents for	Furfural, acetone.
Action on metals	Very slight.
Stability on storage	Stable in steel containers.
Action with water	Insoluble; hydrolyses slowly.
Hydrolysis product	HCl and DM oxide $[NH(C_6H_4)_2As]_2O$. DM oxide is very toxic if swallowed.
Physiological action	Headache, nausea, violent sneezing, followed by temporary physical debility.
First Aid	Breathe low concentrations of chlorine from bleaching powder bottle.
Odor detectable at	Almost no odor to average man.
Intolerable concentration	3 minutes' exposure 0.005 oz./1,000 cu. ft. air.
Lethal concentration	* 30 minutes' exposure; 0.65 oz./1,000 cu. ft. air.
Method of neutralizing	Gaseous chlorine; bleach liquor.
Munitions suitable for use	Candle, burning type shell or air bomb.

* Not obtainable in the open air.

Background Document C, Reference 34

Weast, R.C., 1980, *CRC Handbook of Chemistry and Physics*, CRC Press, Inc., Boca Raton, FL.

This document can be obtained through most local or university libraries.

Background Document C, Reference 35

Williams, A., and I.T. Ibrahim, 1981, "A New Mechanism Involving Cyclic Tautomers for the Reaction with Nucleophiles of the Water-Soluble Peptide Coupling Agent 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)," *J. Am. Chem. Soc.* 103:7,090-7,095.

This document can be obtained through most local or university libraries.